Nos. 24-2274, 24-2277, 24-2278

United States Court of Appeals for the Federal Circuit

JAZZ PHARMACEUTICALS, INC.,
Plaintiff-Appellee,

v.

AVADEL CNS PHARMACEUTICALS, LLC,
Defendant-Appellant.

JAZZ PHARMACEUTICALS, INC.,
JAZZ PHARMACEUTICALS IRELAND LIMITED,
Plaintiffs-Appellees,

v.

AVADEL CNS PHARMACEUTICALS, LLC,
Defendant-Appellant.

JAZZ PHARMACEUTICALS, INC.,
JAZZ PHARMACEUTICALS IRELAND LIMITED,
Plaintiffs-Appellees,

v.

AVADEL CNS PHARMACEUTICALS, LLC,
Defendant-Appellant.

Appeal from the U.S. District Court for the District of Delaware,
Nos. 21-0691, 21-1138, 21-1594, Hon. Gregory B. Williams

CORRECTED NONCONFIDENTIAL OPENING BRIEF OF APPELLANT AVADEL CNS PHARMACEUTICALS, LLC

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November 12, 2024

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Claims 14 and 24 of U.S. Patent No. 11,147,782 (Appx119) recite:

> **14.** A unit dose comprising a formulation of gamma-hydroxybutyrate,
>
> wherein the formulation comprises:
>
> a plurality of immediate release particles comprising gamma-hydroxybutyrate;
>
> a plurality of modified release particles comprising gamma-hydroxybutyrate;
>
> a viscosity enhancing agent; and
>
> an acid;
>
> wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.
>
> ***
>
> **24.** The unit dose of claim **14**, wherein the unit dose is a sachet.

CERTIFICATE OF INTEREST

Case Numbers: 24-2274, 24-2277, 24-2278

Short Case Caption: *Jazz Pharmaceuticals, Inc. v. Avadel CNS Pharmaceuticals, LLC*

Filing Party/Entity: Avadel CNS Pharmaceuticals, LLC, Defendant-Appellant

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: November 12, 2024 Signature: */s/ Gabriel K. Bell*
Name: Gabriel K. Bell

1. Represented Entities. Provide the full names of all entities represented by undersigned counsel in this case. Fed. Cir. R. 47.4(a)(1).

Avadel CNS Pharmaceuticals, LLC

2. Real Party in Interest. Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. Fed. Cir. R. 47.4(a)(2).

None.

3. Parent Corporations and Stockholders. Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. Fed. Cir. R. 47.4(a)(3).

Avadel CNS Pharmaceuticals, LLC is wholly owned subsidiary of Avadel US Holdings, Inc., which is a wholly owned subsidiary of Avadel Pharmaceuticals plc. Avadel Pharmaceuticals plc is a publicly traded company with no parent corporation. Janus Henderson Group plc, a publicly traded company, owns more than 10% of Avadel Pharmaceuticals plc's stock.

4. **Legal Representatives.** List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

Latham & Watkins LLP: Alan J. Devlin, Alex M. Grabowski, David F. Kowalski, Ian R. Conner, Sarah W. Wang, Franco W. Benyamin, Denise Laspina, Kelly Welsh, Ramya Vallabhaneni, Michelle Chin, Bornali R. Borah, Sarah Propst,* Yi Ning,* Laryssa Bedley,* Audra Sawyer.*

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* No longer with firm.

5. **Related Cases.** Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

Yes.

If yes, concurrently file a separate Notice of Related Case Information that complies with Fed. Cir. R. 47.5(b). Please do not duplicate information. This separate Notice must only be filed with the first Certificate of Interest or, subsequently, if information changes during the pendency of the appeal. Fed. Cir. R. 47.5(b).

6. **Organizational Victims and Bankruptcy Cases.** Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

None/Not Applicable.

TABLE OF CONTENTS

Page

Page

TABLE OF AUTHORITIES

Page(s)

CASES

Page(s)

Page(s)

STATUTES

OTHER AUTHORITIES

Page(s)

STATEMENT OF RELATED CASES

These consolidated appeals arise from three combined proceedings in the U.S. District Court for the District of Delaware. *See Jazz Pharmaceuticals, Inc. v. Avadel CNS Pharmaceuticals, LLC*, No. 1:21-cv-00691-GBW (D. Del.); *Jazz Pharmaceuticals, Inc., et al. v. Avadel CNS Pharmaceuticals, LLC*, No. 1:21-cv-01138-GBW (D. Del.); *Jazz Pharmaceuticals, Inc., et al. v. Avadel CNS Pharmaceuticals, LLC*, No. 1:21-cv-01594-GBW (D. Del.). This Court previously decided an appeal arising from one of those actions:

> *Jazz Pharmaceuticals, Inc. v. Avadel CNS Pharmaceuticals, LLC*, No. 23-1186, 60 F.4th 1373 (Fed. Cir. 2023) (Lourie, J, joined by Reyna and Taranto, JJ.) (appeal from D. Del. No. 1:21-cv-00691-GBW).

The following actions may affect or be affected by this Court's decision in the present matter:

> *Avadel CNS Pharmaceuticals, LLC, et al. v. Jazz Pharmaceuticals, Inc., et al.*, No. 1:22-cv-00487-GBW (D. Del.) (filed Apr. 14, 2022);
>
> *Jazz Pharmaceuticals, Inc. v. Avadel CNS Pharmaceuticals, LLC*, No. 1:22-cv-00941-GBW (D. Del.) (filed July 15, 2022); and
>
> *Jazz Pharmaceuticals, Inc. v. Becerra*, No. 1:23-cv-01819-APM (D.D.C.) (filed June 22, 2023).

JURISDICTIONAL STATEMENT

This appeal arises from the district court's entry of an interlocutory order granting a permanent injunction following a jury verdict of patent infringement and further order clarifying the scope of the injunction. *See* Appx1-34; Appx35-37; Appx38-44. This Court has jurisdiction under 28 U.S.C. § 1292(a)(1) and (c)(1). *See Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1146 (Fed. Cir. 2011).

STATEMENT OF ISSUES

1. Whether the district court erred when it granted a permanent injunction prohibiting Defendant-Appellant Avadel CNS Pharmaceuticals, LLC ("Avadel") from implementing the open-label safety extension portion of its existing clinical trial, conducting additional clinical trials, and seeking FDA approval to market its drug, Lumryz, to patients with conditions other than narcolepsy—activities deemed non-infringing under the Patent Act.

2. Whether the district court erred in its *eBay* analysis because (a) the court identified no reason why Avadel's conducting clinical trials and seeking FDA approval would irreparably harm Plaintiff-Appellee Jazz Pharmaceuticals, Inc. ("Jazz") and (b) the court's public interest analysis prematurely presumed that an injunction would not harm the public interest even though it precludes the FDA—the agency assigned to assess public interest in new treatments—from even considering whether Avadel's drug is superior for conditions other than narcolepsy.

INTRODUCTION

District courts presiding over patent cases have the power to enjoin infringing conduct. They may not enjoin conduct that is entirely non-infringing. Here, the district court issued an injunction that prohibits Avadel from fully conducting its existing clinical trial, conducting any other trials, and seeking FDA approval of its innovative new drug, Lumryz, to treat people suffering from idiopathic hypersomnia (IH) or any other condition for which Lumryz is not currently FDA-approved. That injunction rests on clear errors of law. As a matter of express statutory text, any activity "reasonably related to the development and submission of information" to the FDA "shall not be an act of infringement." 35 U.S.C. § 271(e)(1). As this Court has repeatedly explained, this safe harbor provision shields every "activity [that] is reasonably related to obtaining FDA approval" from the application of the patent laws, including conducting clinical trials and making submissions to the FDA. *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1030 (Fed. Cir. 1997); *see also, e.g.*, *Edwards Lifesciences Corp. v. Meril Life Scis. Pvt. Ltd*., 96 F.4th 1347, 1351-52 (Fed. Cir. 2024). Submission of an application for FDA approval does not even require the protection of the safe harbor anyway, since it is not otherwise an act of infringement under Section 271, and is a constitutionally protected form of petitioning the government. The district court may not enjoin these lawful activities. There can be no question that the district court's injunction should be reversed.

Even setting aside that threshold problem, the district court's injunctive order fails because it rests on erroneous, premature reasoning. When the district court enjoined Avadel from seeking FDA approval for IH and other conditions, it assumed the harm to Jazz that would arise from the *marketing* of Lumryz to IH patients was coextensive with the harm to Jazz that would arise from Avadel's *seeking FDA approval* for Lumryz as to IH patients. But the FDA approval process poses no threat of harm to Jazz, and Jazz faces no imminent risk of harm from the marketing of Lumryz. The district court's conclusion that the injunction is necessary to prevent irreparable harm to Jazz is unfounded. Similarly, the district court did not adequately weigh the harm to *Avadel* arising from the injunction. And its public-interest analysis rested on the circular conclusion that Avadel has not yet shown that Lumryz will be especially effective for IH patients—even though the injunction prevents Avadel from making the FDA submissions necessary to make that showing.

The district court's injunction is unlawful. It should be reversed.

STATEMENT OF THE CASE

A. Statutory Background

This appeal turns on the plain language of the Patent Act.

The Definition of Infringement: 35 U.S.C. § 271(a) provides that "[e]xcept as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the

United States any patented invention during the term of the patent therefor, infringes the patent."

The Safe Harbor: In 35 U.S.C. § 271(e)(1), however, Congress provided an exemption: "[i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention … solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." That statutory provision—enacted 40 years ago as part of the Hatch-Waxman Act, *see* Drug Price Competition and Patent Term Restoration Act of 1984, § 202, Pub. L. No. 98-417, 98 Stat. 1585, 1603—was Congress's direct response to this Court's decision in *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 1984).

In *Roche*, the plaintiff (Roche) sought to enjoin a generic pharmaceutical manufacturer (Bolar) from "taking … the statutory and regulatory steps necessary to market … a drug equivalent to a patented brand name drug." 733 F.2d at 860. Specifically, Roche was the manufacturer of Dalmane, a brand-name sleeping pill whose active chemical compound was claimed in a Roche patent. *Id.* Bolar wished to market a generic alternative to Dalmane once Roche's patent expired and—well in advance of that expiration date—"began its effort to obtain federal approval to market its generic version" by importing the patented compound in order to produce

"dosage form capsules" and "'to obtain stability data, dissolution rates, bioequivalency studies, and blood serum studies' necessary for a New Drug Application to the … FDA." *Id.* Roche sued, seeking to enjoin Bolar from using its patented compound "for any purpose whatsoever during the life of" its patent. *Id.* The district court denied Roche's motion for a permanent injunction, holding that "Bolar's use of the patented compound for federally mandated testing was not infringement … because Bolar's use was *de minimis* and experimental." *Id.* at 860-61. This Court reversed, concluding that "Bolar's intended use of [the patented compound] to derive FDA required test data … with a view to the adaption of the patented invention to the experimentor's business is a violation of the rights of the patentee to exclude others from using his patented invention." *Id.* at 863. "We cannot," the *Roche* Court reasoned, "allow a violation of the patent laws in the guise of 'scientific inquiry,' when that inquiry has definite, cognizable, and not insubstantial commercial purposes." *Id.*

Congress's adoption of Section 271(e)(1) reflected its profound disagreement with *Roche*. As the House Committee on Energy and Commerce explained in its report accompanying the legislation, it was "the committee's view that experimental activity does not have any adverse economic impact on the patent owner's exclusivity during the life of a patent." H.R. Rep. No. 98-857, pt. 1, at 46 (1984). Conversely, "prevention of such [experimental] activity would extend the patent

owner's commercial exclusivity beyond the patent expiration date" by preventing competitors from taking the steps necessary to obtain FDA approval of competing products prior to the expiration of the patent. *Id*. It was Congress's wish that there "should be no … direct or indirect method of extending [a] patent term" in this manner. *Id.*

Consistent with Congress's direction, the Supreme Court and this Court have consistently accorded "wide berth" to the scientific experimentation and regulatory activity protected by the Section 271(e)(1) safe harbor. *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 202 (2005). As the Supreme Court has explained, it is "apparent from the statutory text that § 271(e)(1)'s exemption from infringement extends to all uses of patented inventions that are reasonably related to the development and submission of *any* information under the [Food, Drug, and Cosmetic Act]." *Id.* Indeed, the Section 271(e)(1) exemption is not even limited to the "development of information for inclusion in a submission to the FDA." *Id.* at 206. The exemption "leaves adequate space for experimentation and failure on the road to regulatory approval": as long as the "drugmaker has a reasonable basis for believing" that the use of the patented invention, "if successful," would generate information that "would be appropriate to include in a submission to the FDA," then the use is protected by the safe harbor. *Id.* at 207.

This Court has likewise recognized the breadth of the Section 271(e)(1) safe harbor. As this Court has noted, the "statute … does not look to the underlying purposes or attendant consequences of the activity (*e.g.*, tests led to the sale of the patent), as long as the use is reasonably related to FDA approval." *Abtox*, 122 F.3d at 1030. Thus, where a patented invention is used for purposes "reasonably related to FDA approval," that use is categorically permissible, *even if* the user also "disseminat[es] … the data developed for FDA approval" to the public at large such as through the presentation of "clinical trial data at [an industry conference], reporting clinical trial progress to investors, analysts and journalists, and describing clinical trial results in a private fund-raising memorandum." *Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1523-24 (Fed. Cir. 1992). And this Court has reaffirmed that breadth again and again: for example, just a few months ago, this Court recognized that the Section 271(e)(1) safe harbor applies when a user imports infringing products for use at a medical conference where such use "was reasonably related to recruiting investigators for a clinical trial to support FDA approval." *Edwards Lifesciences*, 96 F.4th at 1351.

B. Factual Background

1. Lumryz And The Treatment Of Narcolepsy

This appeal is the latest installment in a long-running litigation between Avadel and its competitor, Jazz, over the market for pharmaceutical oxybate

products that treat narcolepsy and similar conditions. Jazz is the incumbent in that market. *See In re Xyrem (Sodium Oxybate) Antitrust Litig.*, 555 F. Supp. 3d 829, 837 (N.D. Cal. 2021). It markets a drug, Xyrem, that relies on a decades-old formulation to treat narcolepsy. *Id.* Until recently, Xyrem was the only available oxybate treatment for narcolepsy, and Jazz charged monopoly prices. *Id.* In 2020, for example, Medicare paid Jazz an average of over $138,000 per beneficiary for Xyrem prescriptions, for a total cost of over $287 million.[1] That year, Jazz also introduced Xywav, a mixed-salt oxybate formulation for narcolepsy; and later obtained FDA approval for Xywav's treatment of idiopathic hypersomnia (IH), another sleep disorder. *In re Xyrem (Sodium Oxybate) Antitrust Litig.*, No. 20-md-2966, 2023 WL 3440399, at *8 (N.D. Cal. May 12, 2023). But Xyrem and Jazz's successor product, Xywav, have a flaw: they require twice-nightly dosing, forcing patients who suffer from sleep disorders to wake up in the middle of the night every night.

Avadel is a new, single-drug pharmaceutical maker that has developed a once-nightly formulation called Lumryz designed to allow those suffering from narcolepsy to get an uninterrupted night's sleep. Jazz has aggressively sought to prevent the FDA from approving Lumryz. For years, Jazz blocked the FDA from

[1] *See* Ctrs. for Med. & Medicaid Servs., *Medicare Part D Drug Spending by Drug* (2022), https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicaid-spending-by-drug/medicare-part-d-spending-by-drug.

even considering Lumryz for approval by improperly listing a *computer-system* patent in the FDA's Orange Book—a tactic this Court rejected last year, clearing the way for FDA approval of Lumryz to treat narcolepsy. *See Jazz Pharms., Inc. v. Avadel CNS Pharms., LLC*, 60 F.4th 1373, 1376-77, 1382 (Fed. Cir. 2023). The FDA approved Lumryz for the treatment of narcolepsy shortly thereafter and found that Lumryz's single-dose formulation was clinically superior to Xyrem and Xywav for narcolepsy patients. Appx19. Jazz continues to resist the FDA's decision through an ongoing Administrative Procedure Act lawsuit. *See Jazz Pharms., Inc. v. Becerra*, No. 23-cv-01819 (D.D.C.).

2. Avadel's Efforts To Secure FDA Approval For An Idiopathic Hypersomnia Indication For Lumryz

After Avadel secured FDA approval of Lumryz to treat narcolepsy, it turned its attention to obtaining FDA approval for IH. *See* Appx5972-5979 at Appx5977 (Divis Decl. ¶ 13). It began planning for an initial IH clinical trial, called the REVITALYZ trial, Appx5977 (¶ 12), and prepared an initial protocol for the REVITALYZ trial in January 2024. ECF No. 23 (Stern Decl. ¶ 5, Ex. 2). That protocol specified that the trial would be a double-blind, placebo-controlled study incorporating an "open-label safety extension period" of 24 weeks. *Id.* (Stern Decl. Ex. 2 at 4). During the course of that period (the "OLE period"), the protocol calls for seven clinical assessments to check for adverse events and otherwise evaluate the safety of Lumryz for IH patients. *Id.* (Stern Decl. ¶ 5, Ex. 2 at 60-63). As the

FDA has recognized, open-label extensions are an important way of incentivizing patients to enroll in clinical drug trials, generate valuable safety data, and minimize the disruption to the patient of participating in a clinical trial. *See id.* (Stern Decl. ¶¶ 7, 10-12); FDA, *Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs: Guidance for Industry* 13-14 (Nov. 2020), https://www.fda.gov/media/127712/download.[2] On July 31, 2024, Avadel publicly announced "the first patient ha[d] been dosed in REVITALYZ," and noted that the study "will enroll approximately 150 adults who are diagnosed with IH." Press Release, Avadel, Avadel Pharmaceuticals Announces First Patient Dosed in Phase 3 REVITALYZ Trial of Lumryz (sodium oxybate) Extended-Release Oral Suspension for the Treatment of Idiopathic Hypersomnia (July 31, 2024), https://investors.avadel.com/node/13951/pdf; *see also* ECF No. 23 (Stern Decl. ¶ 8). Thus, under the schedule provided for by the REVITALYZ

[2] "Open-label extensions typically occur after a Phase 3 clinical trial of a new treatment. Participants are invited to enroll so that additional safety information can be gathered about long-term use while the [FDA] reviews the treatment for approval." Cystic Fibrosis Found., *After the Clinical Trial: What's Next?*, https://www.cff.org/research-clinical-trials/after-clinical-trial-whats-next (last visited Sept. 29, 2024). Indeed, Jazz's clinical trial for Xywav included an open-label safety extension as well. Nat'l Libr. of Med., *A Multicenter Study of the Efficacy and Safety of JZP-258 in the Treatment of Idiopathic Hypersomnia (IH) With an Open-label Safety Extension*, ClinicalTrials.gov (updated Nov. 24, 2021), https://clinicaltrials.gov/study/NCT03533114.

protocol, the first REVITALYZ study participants will enter the OLE period in early November 2024. ECF No. 23 (Stern Decl. ¶ 8).

At the time that Avadel launched the REVITALYZ study, it projected that the trial would yield a complete set of clinical data in the CBI of CBI. Those data would then be submitted to the FDA for its approval of an IH indication for Lumryz, with commercial sales to follow in approximately the CBI of CBI. *See* Appx5977 (Divis Decl. ¶ 13). Avadel planned to apply for Orphan Drug Exclusivity for Lumryz in IH, as it had done when seeking FDA approval of Lumryz for narcolepsy. Appx5977 (Divis Decl. ¶ 14). Avadel projected that, just as the FDA had found that Lumryz made a major contribution to patient care over Jazz's drug Xywav in the treatment of narcolepsy, so too would the FDA make a similar finding with respect to the treatment of IH. Appx5977 (Divis Decl. ¶ 14).

C. The Present Litigation

Jazz sued Avadel for patent infringement in the present matter in 2021.[3] That proceeding recently culminated in a multi-day jury trial. Before trial, the parties stipulated that Lumryz infringes claim 24 of Jazz's U.S. Patent No. 11,147,782 ('782 patent), directed to a "unit dose" of a formulation of gamma-hydroxybutyrate, "wherein the unit dose is a sachet." Appx119 (cl. 24). The jury rejected Avadel's validity challenges, while also rejecting Jazz's infringement claims under another

[3] Jazz filed three suits that proceeded together below. Appx139 (Dkt. 65).

patent. *See* Appx4380-4391. And the jury rejected Jazz's request for a multi-million-dollar damages figure, instead awarding a modest amount for past infringement of the '782 patent, resulting in an award of just under $233,563. Appx4390.

1. The District Court's Injunction

The district court thereafter announced it would consider Jazz's motion for a permanent injunction before receiving the parties' post-trial motions. Appx4543.[4] Jazz sought a blanket injunction that would prohibit Avadel from marketing Lumryz to anyone other than current patients "through and including the expiration date of the '782 patent, including any … extensions granted thereon." Appx4550 (Injunction Mo.). Although Jazz's proposed injunction included a carveout for "currently-ongoing clinical trials," the proposed injunction otherwise provided that "Avadel may not seek approval from the [FDA] for any indication that was not already part of Lumryz's approved product labeling as of March 4, 2024." Appx4550. This meant that Avadel would not be able to seek FDA approval to market Lumryz to patients suffering from IH (or any other medical condition that

[4] Because the district court has not yet received briefing—much less ruled—on the parties' post-trial motions, Avadel has not yet had the opportunity to present an appeal on the merits of the district court's final judgment. Avadel intends to do so as necessary once the district court has considered and ruled on the parties' post-trial motions. The present appeal solely concerns the district court's interlocutory orders granting Jazz's motion for a permanent injunction, and later expanding its scope.

Lumryz might effectively treat), or to conduct any new clinical trials in connection with such FDA approval.

Avadel opposed on numerous grounds, including on the fundamental ground that, with respect to IH patients, Avadel *cannot* infringe, since it lacks FDA approval to market Lumryz to IH patients and does not market Lumryz to IH patients. Appx9001-9131 at Appx9066 (Injunction Hrg. Tr.). Avadel also explained that, until it obtains FDA approval, its planned testing of Lumryz for IH patients falls within the statutory safe harbor permitting conduct that would otherwise infringe if that conduct is intended to generate data for submission to FDA. Appx9066. Thus, Avadel explained that, as to the clinical-trial and regulatory process for IH patients, there is nothing to enjoin. Appx9077-9079, Appx9087. Avadel also noted that it intends to invest CBI in a clinical trial for IH patients, Appx9064, and underscored that there is good reason companies cannot infringe patents when they are conducting clinical trials—Congress wanted to encourage companies to conduct such trials, Appx9066.

Jazz acknowledged that it was not seeking to enjoin clinical trials and offered no argument that they would fall outside of the protections of the safe harbor. Appx9100-9101. And at the June 4, 2024 injunction hearing, the court acknowledged that Avadel's clinical studies and regulatory submissions are protected by law. Appx9066 (66:24-25).

Yet, on August 27, 2024, the district court issued an injunction undermining that statutory protection. At the outset, the court correctly denied Jazz's motion for injunction as to narcolepsy patients—because, among other things, the FDA already determined Lumryz is "clinically superior" to Xyrem and Xywav for narcolepsy, and there is a strong public interest in "protecting patient access" to Lumryz, Appx19-23. In contrast, the district court granted a broad injunction blocking activities relating to IH. The district court approved an injunction not only prohibiting Avadel from ever marketing Lumryz to IH patients, but also barring Avadel from "seek[ing] approval of Lumryz from the FDA for the treatment of IH." Appx37. And while the order permits Avadel to "continue to use Lumryz in currently-ongoing clinical trials," it bars Avadel from undertaking any new clinical trials. Appx37. Neither the district court's injunction order nor its opinion supporting the order addressed the express statutory safe harbor for the "development and submission of information" to the FDA. 35 U.S.C. § 271(e)(1).

In determining that the *eBay* factors favored an injunction as to IH, the district court reasoned that "Lumryz's entrance into the market for IH would irreversibly harm Jazz's market share," Appx24, and "Jazz has a pointed interest in protecting its market exclusivity," Appx27. The district court relied on such marketing even though it was purely hypothetical, as Avadel does not, and *could not*, market Lumryz until after FDA approval—in CBI at the earliest, as it explained to the district court.

As to the public interest in Lumryz's availability for IH patients, the court—rather than waiting for FDA findings regarding the efficacy of Lumryz for IH patients—weighed the medical benefits of Lumryz's availability for itself, and determined that Lumryz does not offer "any … distinct benefits to patients with IH," Appx30, even though the FDA had concluded the exact opposite as to patients with narcolepsy.

2. Jazz's Construction Of The Injunction And Avadel's Stay Applications

Avadel appealed the next day. In correspondence between the parties, Jazz sought to expand the injunction's scope, arguing that—despite the injunction's clear exclusion of ongoing clinical trials—any continued work on Avadel's ongoing IH clinical study (REVITALYZ) is proscribed by the district court's injunction. According to Jazz, so long as Avadel is enjoined from seeking FDA approval for IH, the safe harbor does not protect activities for that indication. Appx7525. Jazz insisted that Avadel should not take any further action as to IH clinical studies, including enrolling additional subjects in ongoing studies or beginning any proposed open-label safety extension of any ongoing study. Appx7525.

Because the injunction immediately threatened core activities protected under the safe harbor—especially in light of Jazz's unwarranted expansion of the injunction and implicit threat of contempt—Avadel moved for a stay pending appeal in the district court. Appx7493-7527 (Emergency Stay Br.). Avadel explained that the injunction's prohibitions on conducting future clinical trials and seeking FDA

approval cannot stand because those activities are squarely protected under the Patent Act's safe harbor and the First Amendment. And Avadel explained that if the injunction were expanded to bar aspects of its currently-ongoing REVITALYZ study—such as enrolling new patients or providing open-label extensions (OLE)—that, too, would exceed the district court's authority in light of the safe harbor. Appx7503-7505 (Emergency Stay Br.); Appx7528-7533 at Appx7530-7531 (Gudeman Decl. ¶¶ 6-9). Avadel concurrently moved for a stay pending appeal in this Court and for expedited briefing. ECF Nos. 7, 9. Avadel's motion for expedited briefing was granted. ECF No. 13. Its stay motion remains pending in this Court.

3. The District Court's Denial Of A Stay And Expansion Of The Injunction

On September 24, 2024, the district court denied Avadel's stay motion and issued an opinion that discussed and *expanded* the injunction's scope. On one hand, the court clarified that Avadel may proceed with the first part of its ongoing REVITALYZ study and continue to enroll patients up to the targeted 150 volunteers. On the other hand, however, the court held that Avadel could *not* proceed with the second part of its ongoing clinical trial, an "open-label safety extension." Appx41-43; *see* ECF No. 23 (Stern Decl. ¶ 5, Ex. 2); *supra* at 9-10. Notably, the district court did not even attempt to explain how its restrictions on clinical trials and seeking FDA approval are consistent with the safe harbor and First Amendment.

The parties then filed supplemental briefing on the impact of the district court's September 24 order. Avadel explained that OLE is a critical component of the ongoing REVITALYZ study—expressly included in the study's FDA-approved protocol to generate valuable safety data, necessary to incentivize participants, and important to allow continuation of care for existing participants—and thus protected by the safe harbor. ECF Nos. 23, 27. The REVITALYZ protocol calls for collecting data on all "safety endpoints," including adverse events, throughout the "Open-Label Safety Extension" period. ECF No. 23 (Stern Decl. ¶ 5, Ex. 2 at 4, 60-63, 66, 79, Ex. 3 at 4 , 59-62, 65, 78). And Dr. Thomas Stern, one of the principal investigators for Avadel's ongoing trial, explained that the district court's injunction prohibiting open-label extensions will "make recruiting patients significantly more challenging, since those patients would then be facing the prospect of stopping their existing treatment, transitioning onto a new treatment (Lumryz) for 14 weeks, then transitioning back to their original treatment." *Id.* (Stern Decl. ¶ 10). In Dr. Stern's view, the district court's injunction prohibiting an open-label extension will be "highly detrimental to patients enrolled in" the study and, "[a]t a minimum, … delay the results" of the study, and could even "jeopardiz[e] the entire trial." *Id.* (Stern Decl. ¶¶ 12, 15).[5]

[5] On September 27, 2024, Avadel filed amended notices of appeal to encompass the district court's September 24 order.

SUMMARY OF ARGUMENT

The injunctive order exceeds the scope of the district court's authority—sweeping in activities that the Patent Act expressly deems non-infringing—and rests on a misguided assessment of the factors governing issuance of an injunction.

A. 1. When issuing an injunction at the conclusion of a patent-infringement case, a district court may enjoin the defendant to stop the infringing conduct of which the plaintiff complained. The district court has no authority to enjoin conduct that is entirely non-infringing. Here, the district court enjoined activities—conducting clinical trials for its new IH treatment and seeking FDA approval—that are expressly defined as non-infringing under the Section 271(e)(1) safe harbor. Indeed, even setting aside the safe harbor, seeking FDA approval for Avadel's new IH treatment is non-infringing under Section 271(a). And the First Amendment further protects Avadel's efforts to seek FDA approval. The injunction therefore exceeds the district court's authority.

2. Jazz's principal argument is that Avadel somehow waived its reliance on the Section 271(e)(1) safe harbor by failing to plead it as an affirmative defense. That is meritless. The argument asserted here is not a defense to liability for infringement; it is an argument about the proper scope of the district court's injunction. In its complaint, Jazz did not accuse Avadel of infringement as to any of its acts relating to FDA approval; indeed, Jazz affirmatively *disclaimed* infringement

as to any acts protected by the safe harbor. So until Jazz proposed an injunction that would prohibit Avadel from seeking FDA approval of Lumryz for IH patients, Avadel had no basis to raise the safe harbor. At that point, Avadel explained to the district court why any conduct relating to potential FDA submissions was non-infringing and therefore not subject to an injunction. The issue was preserved.[6] And as to the merits, Jazz has made no real effort to show how the district court's injunction can be reconciled with the safe harbor. For good reason: it cannot.

B. Even setting aside the district court's lack of authority, the injunction should be reversed because it rests on a series of errors in the court's analysis of the *eBay* factors governing the issuance of a permanent injunction. The district court treated Jazz's injury on account of Avadel's *marketing* of Lumryz for IH as a sufficient basis for the injunction. But the district court made no findings (nor could it do so) that Avadel's mere submission of information to support an FDA application, nor the application itself, would harm Jazz. The court's treatment of the balance of the equities suffered from related problems. And the court's analysis of the public interest was circular and backwards. Instead of recognizing that Avadel had not yet had the opportunity to demonstrate the clinical superiority of Lumryz for the treatment of IH, the district court faulted Avadel for failing to introduce evidence

[6] Jazz raised waiver in its opposition to the district court stay motion, *see* Appx7542-7545, but the district court did not find any such waiver. Appx38-44.

that Lumryz is more effective than Xywav or Xyrem at treating IH. But until the FDA reviews the evidence from Avadel's clinical trial, it is impossible to come to rest on that question. For these reasons, too, the injunction should be reversed.

STANDARD OF REVIEW

This Court reviews a district court's order granting a permanent injunction for an abuse of discretion. *See SiOnyx LLC v. Hamamatsu Photonics K.K.*, 981 F.3d 1339, 1349 (Fed. Cir. 2020). "A district court abuses its discretion when it acts 'based upon an error of law' … or commits 'a clear error of judgment.'" *Robert Bosch*, 659 F.3d at 1147 (quoting *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1352 (Fed. Cir. 2009)). "To the extent the court's decision is based upon an issue of law, we review that issue de novo." *Id.* at 1148 (quoting *Ecolab*, 569 F.3d at 1352).

ARGUMENT

THE DISTRICT COURT'S INJUNCTION IS UNLAWFUL

This interlocutory appeal does not concern the merits of Jazz's infringement claims against Avadel; those merits await final resolution in the district court and eventual appeal following the entry of final judgment. This appeal concerns only the lawfulness of the permanent injunction entered by the district court. And there can be no doubt that the injunction is unlawful.

A. The Injunction Prohibits Activity That Is Non-Infringing As A Matter Of Law

1. The Patent Act and Federal Rule of Civil Procedure 65 provide district courts with the authority to "grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable." 35 U.S.C. § 283; *see also* Fed. R. Civ. P. 65. In a patent case, "the only acts the injunction may prohibit are infringement of the patent." *Int'l Rectifier Corp. v. IXYS Corp.*, 383 F.3d 1312, 1316 (Fed. Cir. 2004). A district court's power to grant injunctive relief "to prevent violation of patent rights" does not extend to conduct that is entirely "non-infringing." *Additive Controls & Measurement Sys., Inc. v. Flowdata, Inc.*, 986 F.2d 476, 479-80 (Fed. Cir. 1993). The injunction entered here violates that rule.

The district court's injunction prohibits Avadel from "seek[ing] approval of Lumryz from the FDA for the treatment of IH or for any indication that was not already part of Lumryz's approved product labeling as of March 4, 2024." Appx37. It also prohibits Avadel from using Lumryz in any such approval process, except with respect to "currently-ongoing clinical trials and studies." Appx36. And, as elaborated by the district court in its supplemental order clarifying the injunction, it prohibits Avadel from providing the open-label extension component of its currently-ongoing clinical trial (the REVITALYZ study). Appx38-44. Thus, the injunction prohibits Avadel from both undertaking any new clinical studies and

seeking FDA approval. And it prevents Avadel from generating important long-term safety data and incentivizing participation in its ongoing clinical trial through an open-label safety extension. Yet all of those enjoined activities are non-infringing as a matter of express statutory law.

First, the injunction's prohibitions on clinical trials flatly contradicts the Patent Act's safe harbor for uses "reasonably related to the development" of information for FDA approval of a new drug product. Specifically, it "shall not be an act of infringement" to "use" a "patented invention" if such use is "reasonably related to the *development* and *submission* of information under a Federal law which regulates the manufacture, use, or sale of drugs." 35 U.S.C. § 271(e)(1) (emphasis added). That safe harbor "provides a wide berth for the use of patented drugs in activities related to the federal regulatory process." *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 202 (2005). And it has long been recognized that this provision categorically protects clinical trials, *see id.* at 202 n.6, including all uses "reasonably related to recruiting [assistance] for a clinical trial to support FDA approval." *Edwards Lifesciences Corp. v. Meril Life Scis. Pvt. Ltd*., 96 F.4th 1347, 1351 (Fed. Cir. 2024); *see also, e.g.*, *Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1525 (Fed. Cir. 1992); *Momenta Pharms., Inc. v. Amphastar Pharms., Inc.*, 686 F.3d 1348, 1356 (Fed. Cir. 2012). In short, "collection of data necessary for filing an application with the FDA" is "activity squarely within the

safe harbor." *Edwards Lifesciences*, 96 F.4th at 1352. This includes the FDA-approved open-label safety extension portion of clinical trials, which are necessary to generate robust safety data and incentivize participation. The safe harbor plainly disposes of this case.

In *Edwards Lifesciences*, for example, this Court recently held that the safe harbor protected a medical device company's otherwise infringing importation of two transcatheter heart valves for use at a medical conference to help "recruit[ ] investigators" for a clinical trial that would support FDA approval. 96 F.4th at 1351. Here, however, the district court's injunction directly interferes with Avadel's clinical trial itself by prohibiting Avadel's use of an open-label extension to help recruit and retain clinical trial patients, and to track "safety" data concerning long-term use of Lumryz. Appx38-44; *supra* at 9-10, 16-17; ECF No. 23 (Stern Decl. ¶ 7). And the FDA recognizes the benefit of such open-label extensions are two-fold. First, they are useful "to evaluate safety or persistence of effect" of the study drug on the condition. FDA, *Basics of Clinical Trial Design – Design Population, Intervention, Outcomes*, Clinical Investigator Training Course 20 (Dec. 6, 2023), https://www.fda.gov/media/175389/download. Second, they provide a helpful measure for "encourag[ing] participation" in clinical trials, and the FDA advises that clinical-trial sponsors "should … consider" including open-label extensions in clinical trials in order to "improve the enrollment and retention of participants with

rare diseases." FDA, *Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs: Guidance for Industry* 13-14 (Nov. 2020), https://www.fda.gov/media/127712/download. Open-label safety extension programs in FDA clinical trials are plainly "related to the federal regulatory process." *Merck*, 545 U.S. at 202. They are therefore protected by the safe harbor. The district court's injunction prohibiting Avadel's open-label safety extension program—like its injunction barring any further clinical trials—violates the safe harbor.

Second, the Patent Act also makes clear that seeking FDA approval in and of itself is not infringing activity. Indeed, the mere submission of an FDA application and the submission of clinical-trial results to FDA does not qualify as the "use[]" of a "patented invention," and therefore does not qualify as infringement in the first instance. 35 U.S.C. § 271(a).[7] And if there were any doubt on that score, the safe harbor dispels it: "uses reasonably related to the … submission of information" to

[7] Notably, Congress specifically provided that the submission of an abbreviated new drug application to the FDA under section 505(j) of the Food, Drug, and Cosmetic Act is an act of artificial infringement if the purpose of the submission is to obtain approval with respect to "a drug claimed in a patent or the use of which is claimed in a patent." 35 U.S.C. § 271(e)(2)(A). Even so, a court may not enjoin the *submission* or *approval* of the application; rather, it may enjoin the manufacture or sale of the drug sought to be approved, and it may order the effective date of approval to coincide with "the expiration of the patent which has been infringed." *Id.* § 271(e)(4)(A)-(C). An injunction prohibiting a party from seeking FDA approval and preparing clinical-trial data in connection with such approval process is wholly inconsistent with the Patent Act.

the FDA are non-infringing. *Id.* § 271(e)(1). An application for FDA approval *is* a "submission of information" to the FDA, so it is necessarily non-infringing. *Id.*; *see also Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1030 (Fed. Cir. 1997) (safe harbor protects any "use … reasonably related to FDA approval"). The whole point of the safe harbor is to protect all "activities necessary to obtain regulatory approval." *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 671 (1990).

That the injunction is unlawful is confirmed by constitutional law: Avadel has a First Amendment right to petition "administrative agencies" like the FDA, and it would be "destructive of" that right to prohibit Avadel from advocating its "points of view" with the FDA. *Cal. Motor Transp. Co. v. Trucking Unlimited*, 404 U.S. 508, 510-11 (1972); *see also, e.g.*, *IGEN Int'l, Inc. v. Roche Diagnostics GmbH*, 335 F.3d 303, 310 (4th Cir. 2003); *In re Humira (Adalimumab) Antitrust Litig.*, 465 F. Supp. 3d 811, 828 (N.D. Ill. 2020), *aff'd*, 42 F.4th 709 (7th Cir. 2022); *Teva Pharms. USA, Inc. v. Abbott Laboratories*, 580 F. Supp. 2d 345, 361 (D. Del. 2008). A counter-textual reading of the Patent Act that permitted the district court to enjoin Avadel from seeking FDA approval of a drug would raise serious constitutional problems.

These defects with the injunction are sufficient on their own to establish that the injunction is unlawful and must be reversed. Notably, the district court has never—in its initial injunction opinion or its more recent expansion thereof—tried

to square the scope of its injunction with the statutory and constitutional restrictions that Avadel raised. For good reason: the district court's restrictions on clinical trials and seeking FDA approval are squarely foreclosed under established law.

2. Jazz's arguments in defense of the injunction fly in the face of the record and disregard the plain text of the Patent Act.

a. First, Jazz has argued that Avadel somehow waived any reliance on the Section 271(e)(1) safe harbor because Avadel's Section 271(e)(1) argument is an "affirmative defense" that it failed to "plead" or "prove" before the district court. ECF No. 18 at 7-9. Jazz thus asserts that because Avadel did not "plead the safe harbor defense in its answer," Avadel thereby "waive[d]" any reliance on the safe harbor, and this Court "need not consider it further." *Id.* at 7.

That argument lacks merit. The question on appeal is whether the district court exceeded the scope of its authority to grant injunctive relief under Federal Rule of Civil Procedure 65 and 35 U.S.C. § 283 when it issued an injunction that forbids Avadel from seeking FDA approval of Lumryz for IH patients and from undertaking clinical studies in connection with such FDA approval. *See Additive Controls*, 986 F.2d at 479-80 (discussing Rule 65's limits on "broad injunctions" that impermissibly restrain conduct that is "non-infringing"). That question can be answered by comparing the face of the district court's injunctive order with the plain terms of the Patent Act. Submitting a request for FDA approval is not infringement

under Section 271(a) in the first place, and the safe harbor in Section 271(e)(1) expressly treats the activities subject to the injunction—preparing clinical-trial data, including during an open-label safety extension period, and submitting a request for approval to the FDA—as non-infringing. *See supra* at 21-25. These questions of law do not depend on pleading or proof, and do not go to the infringement verdict rendered by the jury at trial; they go to the unlawful scope of the injunction rendered by the district court.

This case is therefore fundamentally different from those in which an infringement defendant asserts that conduct alleged in a plaintiff's complaint of infringement was non-infringing because of the Section 271(e)(1) safe harbor. *See Proveris Sci. Corp. v. Innovasystems, Inc.*, 536 F.3d 1256 (Fed. Cir. 2008); *REGENXBIO Inc. v. Sarepta Therapeutics, Inc.*, No. 20-1226, 2022 WL 609141 (D. Del. Jan. 4, 2022). In cases like those, resolution of that affirmative defense might turn on questions of proof, and should be asserted in a motion to dismiss, motion for summary judgment, or motion for JNOV. But assertion of any such affirmative defense would have been entirely misplaced here, since Jazz's amended complaint specifically disclaimed infringement as to any "acts expressly exempted by 35 U.S.C. § 271(e)(1)." Appx10008 (No. 21-1594 Compl., Prayer for Relief ¶ D). So Avadel had no basis to raise an affirmative defense as to those acts. Furthermore, Jazz never accused Avadel of infringement through an IH clinical trial, nor could it

have done so at or before trial, since Avadel launched its inaugural IH clinical trial only recently (after Jazz disclaimed any intention of seeking injunctive relief as to such clinical trials). Nat'l Libr. of Med., *Safety and Efficacy of FT218 in Idiopathic Hypersomnia (REVITALYZ)*, ClinicalTrials.gov (updated July 29, 2024), https://clinicaltrials.gov/study/NCT06525077?term=NCT06525077&rank=1. The argument advanced by Avadel in this appeal is not that the jury wrongly held Avadel liable for acts of infringement protected by the safe harbor.[8] It is that the district court wrongly used that judgment as the basis to enjoin acts protected by the safe harbor.

To be sure, Avadel preserved the argument that an injunction that reached Avadel's clinical-trial investigations of Lumryz for IH patients (or that reached Avadel's submission of clinical-trial results to the FDA) would violate the Section 271(e)(1) safe harbor. Avadel repeatedly raised the safe harbor at the hearing on Jazz's Rule 65 motion for permanent injunction and explained that its clinical work falls within the safe harbor for all conduct relating to the FDA approval process. *See, e.g.*, Appx9064-9066, Appx9077, Appx9079-9080, Appx9087, Appx9105

[8] Jazz has suggested that Avadel somehow waived the protections of the safe harbor by stipulating to infringement of claim 24 of Jazz's asserted patent. ECF No. 18 at 8. This is specious: as noted above, Jazz itself exempted from the scope of its infringement claim any "acts expressly exempted by" the statutory safe harbor. Appx10008 (No. 21-1594 Compl., Prayer for Relief ¶ D). Avadel could not stipulate to infringement as to acts that Jazz never treated as infringement.

(Injunction Hrg. Tr.); *supra* at 13. Jazz *agreed*, noting that it is "CBI CBI" clinical trials. Appx9101. Thus, Jazz disclaimed any argument in support of the district court's injunction prohibiting clinical trials. *See Well Cell Glob. LLC v. Calvit*, No. 2023-1229, 2023 WL 6156082, at *4 (Fed. Cir. Sept. 21, 2023). And the parties confirmed their views in post-hearing submissions to the district court: Jazz expressly admitted that it had "CBI" that Avadel could conduct IH studies and Jazz acknowledged that its requested injunction would exempt clinical studies. Appx7367 n.1 (emphasis added). That disavowal also amounts to waiver on Jazz's part. *See Rogers v. Wilmington Tr. Co.*, No. 21-1473, 2022 WL 621690, at *1-2 (3d Cir. Mar. 3, 2022). It is deeply ironic that Jazz now accuses Avadel of having waived reliance on the safe harbor. It is Jazz, not Avadel, that waived.

b. The reason Jazz has argued waiver so aggressively is because it has almost nothing to say in defense of the injunction. In its stay briefing, ECF No. 18 at 11-12, Jazz's principal argument on the merits was that Avadel cannot show that the clinical trials and FDA submissions prohibited by the injunction are "reasonably related" to "the development and submission of information" to the FDA. 35 U.S.C. § 271(e)(1). This makes no sense. The filing that Avadel wishes to submit to the FDA for approval of an IH indication is not just "related to"—but indeed *is*—a "submission of information" expressly protected by the safe harbor. *Id.* In fact, such submission does not even require the protection of the safe harbor, as it does not

involve the making or use of a patented invention in the first place. *See id.* § 271(a). Likewise, clinical trials in support of that FDA application are the archetypal form of conduct protected by the safe harbor. *See Merck*, 545 U.S. at 202 n.6. Courts routinely find that FDA-approved studies like Avadel's current IH study are per se protected by the safe harbor. *See Nexell Therapeutics, Inc. v. AmCell Corp.*, 199 F. Supp. 2d 197, 203-05 (D. Del. 2002); *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1282 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993).

Jazz has also argued that Avadel cannot show that Lumryz is a "patented invention" within the meaning of Section 271(e)(1). ECF No. 18 at 12-15 (citing *Proveris*, *supra* and *REGENXBIO*, *supra*). This argument is unfounded. *Proveris*, which addressed whether a piece of laboratory equipment that was not subject to premarket approval was nonetheless protected by the safe harbor, is clearly inapposite. *See Proveris*, 536 F.3d at 1259, 1265. *REGENXBIO* is similar: the "products" at issue there were cultured cells whose use required no FDA approval. *See REGENXBIO*, 2022 WL 609141, at *4. Lumryz is not a piece of lab equipment or a petri dish of cells that may be freely sold or used without FDA approval. It is a drug product whose uses require FDA approval—including with respect to any new IH indication, as Jazz does not dispute. Jazz's argument that the safe harbor no longer applies to Lumryz for IH clinical trials because Lumryz is already FDA-approved for *narcolepsy* patients is meritless. The safe harbor, by its plain terms,

protects any use of a "patented invention … solely for uses reasonably related to the development and submission of information" to the FDA, regardless of whether that patented invention was previously used for a different submission to the FDA. 35 U.S.C. § 271(e)(1). The safe harbor squarely applies here.

Jazz's last argument on the merits is even weaker. Jazz contends that Avadel cannot rely on the safe harbor because it has not shown that the "sole purpose" of its clinical trials is to conduct research leading to the development and submission of information to the FDA. ECF No. 18 at 15-16 (citing *Edwards Lifesciences*, 96 F.4th at 1355). Jazz misreads *Edwards Lifesciences*, which specifically rejected the argument that a court should second-guess clinical trials if there is suspicion of an ulterior motive or intent. *See Edwards Lifesciences*, 96 F.4th at 1351-52. Here, it is clear that Avadel's preparations for an FDA-approved clinical trial are reasonably related to an eventual FDA submission for an IH indication. *See supra* 21-24. That is enough to fall within the safe harbor. *See Edwards Lifesciences*, 96 F.4th at 1351-52. And although Jazz frets that Avadel might try to distribute information about the results of its clinical trials with parties other than the FDA, *see* ECF No. 18 at 15-16, this Court has specifically held that the fact that a party may publicly "disseminat[e] … the data developed for FDA approval"—including by "reporting clinical trial progress to investors, analysts and journalists"—does not withdraw the protections of the safe harbor. *Telectronics*, 982 F.2d at 1523-24. Jazz's argument

on this point, like all of the other arguments it has advanced, runs headlong into long-established law.

Finally—setting aside Jazz's arguments relating to clinical trials—it bears emphasis that Jazz has yet to advance any substantive argument for why the district court could permissibly enjoin Avadel from *seeking FDA approval* for new indications for Lumryz (including a new IH indication). That aspect of the injunction clearly reaches activity that does not constitute infringement under the plain language of Section 271(a) and Section 271(e)(1). *See supra* at 21-25. Thus far, Jazz's only attempt at any sort of explanation for this feature of the injunction is that the district court did not "enjoin seeking FDA approval in a vacuum." ECF No. 18 at 17. Whatever Jazz may have intended for that non-explanation to mean, the fact remains that the injunction prevents Avadel from petitioning the FDA for approval of a drug. That is a clear violation of Section 271 and the First Amendment. *See supra* at 21-25. Jazz does not effectively argue otherwise.

In short, the district court's injunctive order blatantly oversteps its statutory authority to enjoin infringement. *See Int'l Rectifier*, 383 F.3d at 1316. That fault is a sufficient basis for reversal. *Id.* at 1316-17.

B. The District Court's Analysis Of The *eBay* Factors Was An Abuse Of Discretion

The district court's injunction should be reversed for another reason. A permanent injunction should issue only when the plaintiff has established: "(1) that

it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction." *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006). Here, the district court's analysis of the *eBay* factors was plainly inadequate to support the court's injunction.[9] Properly understood, none of the four *eBay* factors—much less all of them—support the district court's injunction. The injunction should therefore be reversed.

1. Jazz cannot establish the first two *eBay* factors because it never established that it suffered (or would suffer) an irreparable injury in connection with Avadel's non-infringing development and submission of an application for FDA approval of a new IH indication for Lumryz. The district court's injunction prohibiting Avadel from filing new applications for FDA approval and from developing clinical-trial data in connection with those applications addresses conduct that cannot possibly harm Jazz.

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[9] Remarkably, with respect to its late-breaking decision to enjoin the open-label safety extension component of Avadel's ongoing clinical trial, the district court simply did not consider the *eBay* injunction factors. *See* Appx38-44. In that regard, the district court's injunction is entirely unexplained and may be vacated on that basis alone. *See Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1352 (Fed. Cir. 2009).

In demonstrating irreparable harm for purposes of the *eBay* analysis, a plaintiff must "show that it is irreparably harmed *by the infringement*," which requires proof of a "causal nexus" establishing that "the infringement causes the harm." *Apple Inc. v. Samsung Elecs. Co.*, 809 F.3d 633, 639 (Fed. Cir. 2015) (emphasis added). In other words, an injunction may be entered against a defendant only "on account of a harm resulting from the defendant's wrongful conduct, not some other reason." *Id.* at 640.

The injunction issued by the district court did not satisfy that causal nexus requirement. The court reasoned that "Lumryz's entrance into the market for IH would irreversibly harm Jazz's market share and damage its ability to build its reputation as the exclusive market leader." Appx24. It therefore held that "Jazz would suffer irreparable injury if Avadel is not enjoined from seeking FDA approval and marketing Lumryz for IH." Appx24. This does not follow. Accepting for the sake of argument the district court's findings regarding the irreparable harm Jazz might suffer if Avadel *markets* Lumryz to IH patients, that does not establish Jazz would suffer irreparable harm merely because Avadel conducts clinical studies and submits those clinical studies to the FDA for approval. The district court made *no* findings establishing that mere submission of an application for FDA approval—much less the completion of clinical studies in preparation of that submission—would irreparably harm Jazz. *See* Appx24-26. Nor could it have done so, since that

conduct is non-infringing as a matter of law. *See* 35 U.S.C. § 271(e)(1); *supra* at 21-25. It would therefore have been impossible for the district court to have drawn a causal nexus between "the infringement" and any harm purportedly redressed by the injunction. *See Apple*, 809 F.3d at 639.

On top of that problem is another one, just as fundamental: the threat of any harm to Jazz from the *marketing* of Lumryz to IH patients is (at this point) entirely hypothetical and speculative, since Avadel is well over a year away from submitting an application for FDA approval, and even further away from *obtaining* FDA approval to market Lumryz to IH patients. As the Supreme Court has explained, an award of "permanent injunctive relief" is inappropriate where such relief is "not now needed to guard against any present or imminent risk of likely irreparable harm." *Monsanto Co. v. Geertson Seed Farms*, 561 U.S. 139, 162 (2010); *see also, e.g.*, *Ctr. for Food Safety v. Vilsack*, 636 F.3d 1166, 1173 (9th Cir. 2011). Jazz's possible injury from the (as yet impossible) marketing of Lumryz to IH patients is neither a "present" nor "imminent" injury. It is therefore not a suitable basis for establishing an irreparable injury for purposes of *eBay*.

Because Jazz did not establish that the district court's injunction would redress an irreparable harm to Jazz, its case for an injunction failed on the first two prongs of the *eBay* analysis. *See eBay*, 547 U.S. at 391 (requiring (1) a showing of irreparable injury that is (2) not compensable through remedies at law); *cf. Acumed*

LLC v. Stryker Corp., 551 F.3d 1323, 1326-27 (Fed. Cir. 2008) (noting that the first two *eBay* prongs may be analyzed in tandem).

2. The district court's analysis of the balance of the equities also failed for similar reasons. In its opinion, the district court noted that, in the event of an injunction, "Avadel cannot allege [irreparable] injury with respect to the IH market, where Avadel still lacks FDA approval to sell Lumryz." Appx27. But by cutting off Avadel's ability to prepare for and seek FDA approval of Lumryz as to IH patients, the district court deprived Avadel of the chance to line up FDA approval in advance of the expiration of the '782 patent, thus conferring an indirect extension of Jazz's patent term—precisely the harm that Congress sought to avoid when it enacted Section 271(e)(1). *See Eli Lilly*, 496 U.S. at 670; H.R. Rep. No. 98-857, pt. 1, at 46 (1984). The district court entirely failed to consider this problem, even though Avadel advised the court of Congress's clear interest in assuring that clinical experimentation could proceed in the face of existing patent rights. Appx9066 (Injunction Hrg. Tr.).

As to the balance of equities, the district court also reasoned that Avadel could not be harmed by an injunction because it had "concede[d] that it 'has not yet started [any] clinical trial[s]' and would not do so if an injunction was granted." Appx27. That conclusion overlooked Avadel's uncontested evidence showing that it would already have begun—and perhaps even completed—its IH clinical trial work if

"Avadel had obtained FDA approval for Lumryz" as to narcolepsy patients in 2021, "as we were originally expecting" before Jazz improperly "used its computer REMS patent to delay and then to block the FDA from approving Lumryz" for narcolepsy. Appx5977 (Divis Decl. ¶ 13). The district court's conclusion that Avadel's interest in seeking FDA approval was outweighed by Jazz's "interest in protecting its market exclusivity," Appx27—a legal interest that does not extend to the suppression of scientific research and regulatory submissions to the FDA, *see* 35 U.S.C. § 271(e)(1)—was unfounded.

3. Finally, the district court's analysis of the *eBay* public-interest factor inverted the public-interest considerations at stake in this case. In the district court's telling, "Avadel had the burden to prove that enjoining Lumryz for IH would result in a harm to the public that outweighs the public's competing interest in incentivizing" new drug development, yet "Avadel failed to show that Lumryz is a superior or unique treatment for IH." Appx31. That is mistaken: when seeking a permanent injunction, it is the *plaintiff* (Jazz) that bears the burden of establishing that the public interest would not be "disserved" by an injunction. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1381 (Fed. Cir. 2017) (quoting *eBay*, 547 U.S. at 391). And the irony here is that, by delaying Avadel's clinical-trial work for IH patients and preventing Avadel from seeking FDA approval, the district court prevented Avadel from marshaling the record necessary to show that Lumryz is a superior and unique

treatment for IH. Instead, the district court relied on scattered record evidence to draw its own conclusions about clinical superiority. *See* Appx28-30.

That was error. It is the FDA's responsibility to evaluate the efficacy and superiority of new drugs, and there is a manifest public interest in the clinical investigation and expert administrative review that goes into the FDA approval process. That process yields data about the efficacy of pharmaceutical products and unlocks new information that can save and improve lives. Regardless of whether the *marketing* of Lumryz to IH patients should be enjoined during the term of the '782 patent, there is unquestionably a strong public interest in the *investigation and evaluation* of Lumryz's efficacy as to IH patients during that patent term. That public benefit comes at no cost to the patent holder. Again, that is exactly why Congress established the Section 271(e)(1) safe harbor. *See* H.R. Rep. No. 98-857, pt. 1, at 46. Yet the district court's injunction will cut out the FDA and prevent that evaluation from occurring—and the district court did not even consider that harm to the public interest in its order granting an injunction. *See* Appx27-31.

Relatedly, the district court's evaluation of the public interest in Lumryz's availability was premature. It is not possible to weigh the public benefit of Lumryz's availability for IH patients (or the detriment of its exclusion from the IH market) until expert clinicians have evaluated the efficacy of Lumryz vis-à-vis Xywav, the only other FDA-approved treatment for IH. If Avadel is permitted to submit clinical-

trial results to the FDA in connection with an application for approval, the FDA will necessarily consider whether Lumryz "makes a major contribution to patient care over Xywav." Appx5977 (Divis Decl. ¶ 14). But in the absence of that FDA evaluation, the district court is ill-equipped to weigh for itself the relative public benefit or detriment of Lumryz's availability. The district court's abbreviated (and speculative) discussion of the evidence concerning Lumryz's efficacy relative to Xywav, *see* Appx28-30, highlights the dangers of freelance judicial factfinding in this area.

Indeed, the district court *denied* an injunction as to narcolepsy patients precisely because the FDA determined that Lumryz was a superior alternative to Jazz's offerings, Appx19-23, and the FDA's determination "strongly indicates" where the public interest lies, Appx21. The same logic prescribes that the district court should have given the FDA the chance to weigh in on the public interest as it relates to IH patients before issuing an injunction.

* * *

This appeal is straightforward. A district court faced with a claim of patent infringement may enjoin only infringing activity. In 1984, Congress expressly defined the development and submission of information relating to the FDA approval process for drugs as non-infringing. That unquestionably includes conducting clinical trials and seeking FDA approval for new and improved treatment

methods—such as Avadel's treatment of IH with Lumryz—that stand to benefit patients and the public. Yet the district court in this case enjoined such non-infringing activity without regard to the safe harbor established by Congress. Because the court's injunction clearly exceeded the limits of the court's injunctive powers, and the district court's analysis of the *eBay* factors was legally flawed, the injunction cannot stand.

CONCLUSION

The district court's orders enjoining Avadel should be reversed.

Dated: November 12, 2024

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to Federal Rule of Appellate Procedure 32(g)(1) and Federal Circuit Rule 32(b)(3), I hereby certify that the foregoing brief complies with the type-volume limitation in Federal Circuit Rule 32(b)(1) because it contains 9,642 words, excluding the exempted parts under Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b)(2).

I further certify that this response complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5)-(6) because this response was prepared using Microsoft Word 365 in 14-point Times New Roman font.

/s/ Gabriel K. Bell
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CERTIFICATE OF COMPLIANCE WITH RULE 25.1(e)(2)

I hereby certify that the foregoing complies with the limitations set forth in Federal Circuit Rule 25.1(d)(1)(A) and contains 13 unique words (including numbers and images) marked as confidential.

Date: November 12, 2024

/s/ Gabriel K. Bell
Gabriel K. Bell

ADDENDUM

ADDENDUM TABLE OF CONTENTS

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS LLC, Defendant.	C.A. No. 21-691-GBW [redacted]
JAZZ PHARMACEUTICALS, INC. and JAZZ PHARMACEUTICALS IRELAND LIMITED, Plaintiff, v. AVADEL CNS PHARMACEUTICALS LLC, Defendants.	C.A. No. 21-1138-GBW [redacted]
JAZZ PHARMACEUTICALS, INC. and JAZZ PHARMACEUTICALS IRELAND LIMITED, Plaintiff, v. AVADEL CNS PHARMACEUTICALS LLC, Defendants.	C.A. No. 21-1594-GBW [redacted]

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MEMORANDUM OPINION

August 27, 2024
Wilmington, Delaware

GREGORY B. WILLIAMS
UNITED STATES DISTRICT JUDGE

On May 12, 2021, Plaintiffs Jazz Pharmaceuticals Inc. and Jazz Pharmaceuticals Ireland Limited (collectively, "Plaintiffs" or "Jazz") sued Defendant Avadel CNS Pharmaceuticals LLC ("Defendant" or "Avadel") for patent infringement. D.I. 1. Prior to trial, Avadel stipulated that its product, Lumryz, infringed claim 24 of U.S. Patent No. 11,147,782 ("the '782 patent"). Shortly thereafter and following a one-week trial, the jury returned a verdict of no invalidity for lack of written description or enablement and no invalidity for improper inventorship.[1] Now pending before the Court is Jazz's Motion for a Permanent Injunction and for an Ongoing Royalty. D.I. 586.[2] Avadel opposes the Motion for a Permanent Injunction and contends that Jazz is not entitled to an ongoing royalty or, alternatively, is entitled to a royalty at an ongoing rate of 3.5%. D.I. 601 at 1-2. The Court held a hearing on the Motion on June 6, 2024.[3] Having reviewed the Motion and all related briefing, the Court hereby **GRANTS-IN-PART** and **DENIES-IN-PART** Jazz's Motion as follows: (1) Jazz's request for a limited permanent injunction prohibiting Avadel from seeking FDA approval and marketing Lumryz for the treatment of idiopathic hypersomnia ("IH") is **GRANTED**; (2) Jazz's request for a limited permanent injunction prohibiting the use of Lumryz for new patients in the narcolepsy market is **DENIED**; and (3) Jazz's motion for an ongoing royalty for future infringement in the narcolepsy market is **GRANTED**, pending additional briefing on the appropriate rate.

[1]Trial Tr. ("Tr.").
[2]All D.I. cites in this Opinion refer to the docket in Case No. 21-cv-00691-GBW.
[3]Permanent Injunction Hearing Transcript ("P.I. Tr.").

I. LEGAL STANDARD

"According to well-established principles of equity, a plaintiff seeking a permanent injunction must satisfy a four-factor test before a court may grant such relief." *eBay Inc. v. MercExchange, LLC*, 547 U.S. 388, 391, 126 S.Ct. 1837, 164 L.Ed.2d 641 (2006). Under this four-factor *eBay* test, a plaintiff must show by a preponderance of the evidence: "(1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction." *Id.*

II. ANALYSIS

1. Permanent Injunction

Jazz seeks a limited permanent injunction to bar the marketing and sale of Lumryz in two markets: the narcolepsy and IH markets. D.I. 587 at 1. Jazz does not seek to enjoin Avadel from continuing to make, use, or sell Lumryz for patients who, at the time of the injunction, have already been prescribed Lumryz. *Id.* For the following reasons, the Court grants a limited injunction prohibiting Avadel from seeking FDA approval and marketing Lumryz for the treatment of IH. With respect to the market for narcolepsy, however, Jazz has not shown that it is entitled to an injunction restraining the use or sale of Lumryz for new narcolepsy patients. To compensate Jazz for Avadel's continued infringement in the narcolepsy market, the Court grants Jazz's request for ongoing royalties at a rate to be determined for any future infringing sales of Lumryz to patients with narcolepsy.

A. The *eBay* Factors Weigh Against Enjoining Lumryz for Narcolepsy Treatment.

1. *Irreparable Harm*

a. *Jazz established that it suffered some irreparable harm through past loss of market share and price erosion.*

To show irreparable harm, a patentee must prove "1) that absent an injunction, it will suffer irreparable harm, and 2) that a sufficiently strong causal nexus relates the alleged harm to the alleged infringement." *Apple Inc. v. Samsung Elecs. Co.*, 695 F.3d 1370, 1374 (Fed. Cir. 2012). Jazz contends that the prescription of Lumryz for narcolepsy has and would continue to cause Jazz irreparable injury by limiting its market share, eroding the prices of its oxybate products, and damaging its reputation as a "market leader" in narcolepsy treatment. D.I. 587 at 3-8.

The Court agrees that Avadel's infringement has caused Jazz to suffer loss of market share. *See id.* at 3-5. Indeed, there is no dispute that Lumryz competes directly with Jazz's oxybate products in the narcolepsy market, and Avadel's CEO, Gregory Divis, testified during trial that one of Avadel's "primary goals and strategies" is to target Jazz customers by educating physicians on the benefits of switching patients from Xyrem and Xywav to Lumryz. Tr. 501:1-11, 524:21-23; P.I. Tr. 13:14-23 (noting that Avadel's marketing targeted prescribers and "advocated for them to switch patients from Jazz's products to Lumryz"). Avadel's internal reporting shows that Avadel succeeded in its efforts to switch Jazz patients to Lumryz, as approximately 74% of patients on Lumryz in 2023 were "switch patients with more coming from the [Xywav] mixed salt." Tr. 523:17- 524:20; Jazz Ex. 2 at 10-12. Jazz's internal records similarly found that prescriptions for Lumryz were "coming from switched patients instead of discontinued Jazz patients." P.I. Tr. 14:4-21; Honerkamp Decl., ¶¶ 25-26.

[redacted] *See Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1382 (Fed. Cir. 2006) (finding irreparable injury where patentee was "forced to offer discounted rates and price concessions to third-party payors, such as health maintenance organizations, in order to keep [its product] on a favorable pricing tier, which governs what consumers pay for that drug").

Because Jazz and Avadel continue to compete directly in the narcolepsy market, the evidence that Avadel negotiated PBM agreements to [redacted] coupled with evidence that Jazz prioritized marketing campaigns aimed at switch patients "strongly suggests irreparable harm." *Natera Inc. v. ArcherDx, Inc.*, No. 20-CV-125-GBW, 2023 WL 9103876, at *3 (D. Del. 2023)(finding irreparable harm where patentee and infringer are direct competitors

and patentee has lost market share due to competition); *see also Presidio Components, Inc. v. Am. Tech. Ceramics Corp.*, 702 F.3d 1351, 1363 (Fed. Cir. 2012) ("Direct competition in the same market is certainly one factor suggesting strongly the potential for irreparable harm without enforcement of the right to exclude."). Moreover, as Avadel recently reported that Lumryz has the potential to take 50-60% of the oxybate-treated market, there is at least some continued risk of loss of market share and price erosion if Avadel's use of Lumryz is not enjoined. *See* Tr. 525:16-527:25.

Nevertheless, Jazz's claims of irreparable harm are undermined to a degree by Jazz's public statements and filings which attribute some of Jazz's market share loss and price erosion to generic competition. Jazz admitted in recent SEC filings, for instance, that "a significant percentage of the prescriptions written for Xyrem" will be filled with generic manufacturers. Jazz Ex. 4 at 17, 36. While Jazz conceded during the Permanent Injunction Hearing that "some of the lost sales of Xyrem are coming from generic sales," Jazz failed to quantify the effects of generic sales on the market for Xyrem and maintained that its licenses to generic manufacturers would not affect demand for Xywav. P.I. Tr. 51:16-24 (arguing that does "not touch Xywav; it has nothing to do with Xywav"). Yet, in its SEC filings, Jazz recognized that generic oxybate sales "have negatively impacted and ***are expected to continue to negatively impact Xyrem and Xywav sales for patients with narcolepsy***." Jazz Ex. 4 at 17, 36 (emphasis added). In a recent 10-Q, Jazz similarly noted that "generic or AG high-sodium oxybate products or branded high-sodium oxybate entrants in narcolepsy, such as Avadel's Lumryz, have had and may continue to have the effect of changing payor or formulary coverage of Xywav or Xyrem in favor of other products, and indirectly adversely affect sales of Xywav and Xyrem." Avadel Ex. 6 at 38; *see*

also Jazz Ex. 4 ("Generic competition can decrease the net prices at which branded products, such as Xywav and Xyrem are sold.").

Given these public statements, the Court cannot disregard Jazz's generic licenses merely because they cover "unrelated patents covering Xyrem and Xywav . . . ." D.I. 610 at 4. Indeed, the Federal Circuit has explained that "'[t]he fact of the grant of previous licenses, the identity of the past licensees, the experience in the market since the licenses were granted, and the identity of the new infringer *all may affect* the district court's discretionary decision concerning whether a reasonable royalty from an infringer constitutes damages adequate to compensate for the infringement.'" *Nichia Corporation v. Everlight Americas, Inc.*, 855 F.3d 1328, 1343-44, 122 U.S.P.Q.2d (Fed. Cir. 2017) (internal citations omitted & emphasis added). The district court in *Nichia* considered that the patentee granted licenses to "'significant competitors' who posed 'major threats' to [the] flagship products." *Nichia Corp. v. Everlight Elecs. Co.*, No. 02:13-CV-702-JRG, 2016 WL 310142, at *66 (E.D. Tex. Jan. 25, 2016), *aff'd sub nom. Nichia Corp. v. Everlight Americas, Inc.*, 855 F.3d 1328 (Fed. Cir. 2017). In finding that such evidence weighed against irreparable harm, the district court noted that the licenses changed the market by making available "multiple low-priced non-infringing alternatives." *Id.* The Federal Circuit found "no clear error in the district court's finding . . . ." *Nichia*, 855 F.3d at 1344.

Similarly, here, Jazz's licenses impact the narcolepsy market by allowing generic oxybate products to enter the market and compete directly with Xyrem, Xywav, and Lumryz. Dr. Rainey, Jazz's damages expert, recognized that the licenses would create "a highly competitive environment." Rainey Tr. 67:16-23. As highlighted above, Jazz's public filings also reveal that Jazz attributed some past and future market share loss and price reduction to this generic competition. *See supra* at 5. While Jazz's licenses to generic manufacturers do not establish a

lack of irreparable harm per se,[4] these licenses undermine Jazz's effort "to lay all the blame for lost sales and price erosion on Avadel." D.I. 587 at 4. Indeed, in requesting a limited injunction, Jazz failed to distinguish or quantify the past and future market share loss and price erosion caused directly by Avadel's infringement from the harm attributable solely to generic competition. *See* D.I. 610 at 3 (maintaining that the licenses are "irrelevant"). If Jazz expects that generic manufacturers will have significant implications for its oxybate products in the narcolepsy market, as Jazz's public filings imply, this refusal to meaningfully address the impact of generic competition, at the very least, casts doubt on Jazz's claim that enjoining Lumryz would remedy most or any of the asserted future injury. *See Nichia*, 2016 WL 310142, at *66 ("[B]ecause there are multiple low-priced non-infringing alternatives from competitors available to replace the accused [] products if such products were not available, Nichia America has failed to establish the amount of any additional supposed sales, if any, in the absence of competition from Everlight. Nichia has failed to establish it will suffer irreparable harm in the absence of an injunction.").

Further, Jazz contends that, absent an injunction, Avadel's marketing strategy will cause irreparable harm to Jazz's reputation and goodwill. D.I. 587 at 7-8. Yet, Jazz's claims of reputational harm are unpersuasive for at least three reasons. First, Jazz does not practice claim 24 of the '782 patent. While the Court agrees that irreparable harm may result even where the patentee does not practice the patent-in-issue,[5] "[r]eputational harm has previously been found to weigh in favor of injunctive relief where a plaintiff was itself practicing the patented invention

[4] *Acumed*, 551 F.3d at 1328.

[5] *See Presidio*, 702 F.3d at 1363 ("Even without practicing the claimed invention, the patentee can suffer irreparable injury.").

and where there was evidence of consumer confusion, a loss of product distinctiveness, or some risk to that plaintiff's status as an innovator." *Baxalta Inc. v. Genentech, Inc.*, No. CV 17-509-TBD, 2018 WL 3742610, at *11 (D. Del. Aug. 7, 2018). Where, on the other hand, the patentee does not practice the patent-at-suit, reputational harm is unlikely because "there is no risk that consumers will be confused about the source of the various products." *Id.* Second, as Jazz seeks to enjoin the use and sale of Lumryz for patients who have never been prescribed Lumryz, the injunction "will not stop doctors and patients from associating the innovation of [Lumryz] with [Avadel]." *Id.* And an injunction may even harm Jazz's reputation "if doctors know they're trying to keep Lumryz from [new] patients who can benefit from it quite a bit." *Id.* (internal citations omitted). Finally, as to Avadel's marketing of Lumryz as the superior treatment for narcolepsy, Jazz fails to show how Avadel's marketing campaign "is causing actionable reputational harm" when Avadel's superiority claims are supported by the FDA's ODE determination. *Abbott Cardiovascular Sys., Inc. v. Edwards Lifesciences Corp.*, No. CV 19-149 (MN), 2019 WL 2521305, at *22 (D. Del. June 6, 2019).[6]

b. *There is a sufficiently strong nexus between the irreparable harm and Avadel's infringement.*

Avadel contends that Jazz fails to establish a causal nexus between its alleged irreparable harm and Avadel's infringement. D.I. 601 at 11-13. The Court disagrees. The goal of the causal nexus requirement is to ensure that there is "*some* connection" between the harm alleged and the infringing acts, and the analysis of this requirement is a "flexible" one. *Apple, Inc. v.*

[6]Jazz also fails to present any evidence that Avadel's attempts to "downplay[] the FDA's sodium finding" is likely to result in irreparable harm. "[S]imply assert[ing]" that the marketing campaign will damage Jazz's reputation is not sufficient to establish irreparable harm. *Abbott*, 2019 WL 2521305, at *22; *but see Natera*, 2023 WL 9103876, at *3 (presenting evidence that customers "started asking questions why that happened is there something wrong with Natera").

Samsung Elecs. Co., 735 F.3d 1352, 1364 (Fed. Cir. 2013) (emphasis added). A patentee can therefore satisfy the nexus requirement in a number of ways—including, for example, "with evidence that a patented feature is one of several features that cause consumers to make their purchasing decisions[,]" "evidence that the inclusion of a patented feature makes a product significantly more desirable[,]" and "evidence that the absence of a patented feature would make a product significantly less desirable." *Id.*

Avadel argues, however, that Jazz must show that Lumryz "contains no feature relevant to consumers' purchasing decisions other than what the ['782] patent claims." D.I. 601 at 12. While "a finding that the competitor's infringing features drive consumer demand for its products satisfies the causal nexus inquiry[,] . . . this rule is neither categorical nor is it mechanically applied." *Endo Pharms. Inc. v. Amneal Pharms., LLC*, No. 12 CIV. 8060 (TPG), 2016 WL 1732751, at *5 (S.D.N.Y. 2016). Indeed, in cases where evidence of customer demand for an "infringing feature" has satisfied the nexus requirement, the relevant products have been "'complex, multi-featured' products." *Janssen Prod., L.P. v. Lupin Ltd.*, 109 F. Supp. 3d 650, 700 (D.N.J. 2014), *modified on other grounds*, No. 10-5954 (WHW), 2016 WL 1029269 (D.N.J. 2016); *Genband US LLC v. Metaswitch Networks Corp.*, 861 F.3d 1378, 1384 (Fed. Cir. 2017) ("The clarified standards set forth in *Apple III* and *Apple IV* govern the causal-nexus inquiry, at least in a multi-purchaser, multi-component situation in which only a component of a larger product or system is covered by the patent in suit."). Here, however, the infringing product is a pharmaceutical with a formulation that wholly infringes claim 24, which means that Avadel could not launch Lumryz as a commercial product without Jazz's invention. Under these circumstances, it is impracticable for Jazz to treat the infringing aspects of Lumryz "as a small

component part" of the overall drug.[7] Thus, the Court will not require Jazz to identify a non-prior art "feature" to satisfy the nexus requirement. *See also Janssen*, 109 F. Supp. 3d at 700 (noting that the nexus requirement does not require the patentee to "put forth [] evidence that the claimed, non-prior art elements of the [] patent are what drive sales or consumer demand" in the case of a process patent for a pharmaceutical, given that "it is not possible to separate the process for making the finished [] product from the product itself in evaluating consumer demand and nexus").

Rather, in this matter, the nexus requirement is satisfied by the indisputable evidence of direct competition between the parties. *See Endo Pharms.*, 2016 WL 1732751, at *5 ("Competition is logically tied to injury, since directly competitive companies are most likely to be rivals for market share, sales, customers, profits, business opportunities, goodwill, and brand power."); *see also Brocade Communications Systems, Inc. v. A10 Networks, Inc.*, 2013 WL 140039, *3-*4 (N.D. Cal. 2013) (finding that patentee "has proven a sufficient nexus between the established infringement and irreparable harm from the loss of its exclusive right to practice its patents"). Indeed, the weight of the evidence reveals that Avadel intended to introduce a competing product and recognized that Lumryz would impact the market demand and the prices for Jazz's products. *See, e.g.*, Jazz Ex. 2 at 23. Thus, the Court is persuaded that there is at least "some connection" between the alleged irreparable harm and Avadel's infringement.

In sum, Jazz has presented evidence of past harm due to market share loss and the erosion of the price for Jazz's products and has shown that a sufficient nexus exists between this harm

[7] And even if Jazz could treat the infringing elements as a "feature," the formulation of a pharmaceutical is typically what drives demand. D.I. 610 at 3 (citing *AstraZeneca AB v. Apotex Corp.*, 782 F.3d 1324, 1337-40 (Fed. Cir. 2015)).

and Avadel's infringement. While "[p]ast harm to a patentee's market share[] [and] revenues" is relevant to a finding of irreparable injury,[8] here, the magnitude of Jazz's past harm—and, more importantly, the likelihood that Avadel's infringement would continue to result in such harm—is uncertain given that at least some of the harm alleged by Jazz is attributable to generic competition. Considering the clear evidence of past harm in light of Jazz's attempts to dismiss the effects of generic competition, the Court finds that this factor, at most, weighs only slightly in favor of a permanent injunction. *See Advanced Cardiovascular*, 579 F. Supp. 2d at 560 (finding no irreparable harm where "[patentee] has not addressed the fact that [a third-party competitor] holds a larger market share than [defendant]").

2. *Inadequacy of Legal Remedy*

The second *eBay* factor "is nearly indistinguishable from irreparable injury" and asks whether legal remedies are adequate to compensate the patentee for the harm caused by the infringing conduct. *Natera*, 2023 WL 9103876, at *4. Avadel contends that this factor weighs against a permanent injunction because "Jazz has willingly licensed its Xyrem and Xywav patents to ten different direct competitors, for a zero percent royalty." D.I. 601 at 15. For the reasons discussed *supra*, the Court agrees that Jazz's willingness to forego its patent rights for compensation with generic manufacturers, despite the likely impact generic sales would have on Jazz's business, "supports [a] [] conclusion that [Jazz] will not suffer irreparable harm absent an injunction." *Advanced Cardiovascular Sys., Inc. v. Medtronic Vascular, Inc.*, 579 F. Supp. 2d 554, 560 (D. Del. 2008), *dismissed*, 356 F. App'x 389 (Fed. Cir. 2009). However, Jazz's willingness to license to generic competitors "is but one factor for the [Court] to consider." *Acumed LLC v. Stryker Corp.*, 551 F.3d 1323, 1328 (Fed. Cir. 2008) ("[T]he amount of weight

[8] *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 861 (Fed. Cir. 2010).

given to a patentee's prior willingness to grant licenses is solely within the discretion of the district court.").

Also relevant to the Court's analysis is the evidence of at least some past market share loss and price erosion, which typically "suggests that mere damages will not compensate for a competitor's increasing share of the market." *Douglas Dynamics, LLC v. Buyers Prod. Co.*, 717 F.3d 1336, 1345 (Fed. Cir. 2013); *E.I DuPont de Nemours & Co. v. Unifrax I LLC*, No. 14-1250, 2017 WL 4004419, at * 5 (D. Del. Sept. 12, 2017), *aff'd*, 921 F.3d 1060 (Fed. Cir. 2019); *Natera*, 2023 WL 9103876, at *4 (Internal citations omitted) (finding that "'loss of market share, brand recognition, and customer goodwill,' . . . demonstrate inadequacy of monetary damages"). Having considered the record before it, the Court finds that legal remedies may be inadequate to compensate Jazz for the past irreparable harm caused by Avadel's infringement. This factor therefore weighs slightly in favor of an injunction.

3. *Balance of the Equities*

"To satisfy the third *eBay* factor, the patentee must show that the balance of hardships weighs in its favor." *Apple Inc. v. Samsung Elecs. Co.*, 809 F.3d 633, 645 (Fed. Cir. 2015) (citing *eBay*, 547 U.S. at 391). "This factor 'assesses the relative effect of granting or denying an injunction *on the parties*.'" *Id.* (quoting *i4i*, 598 F.3d at 862) (emphasis added). "As a preliminary matter, the balance considered is only between a plaintiff and a defendant, and thus the effect on customers and patients alleged by [the infringer] is irrelevant under this prong of the injunction test." *Acumed*, 551 F.3d at 1330. However, the Court may consider "the parties' sizes, products, and revenue sources." *i4i*, 598 F.3d at 862-63.

Here, Avadel maintains that the balance of hardship weighs against an injunction because Jazz "faces no existential risks in the absence of an injunction" while "[redacted]

[redacted]" D.I. 601 at 17. Jazz, in contrast, contends that its "resulting lost market share and being forced to compete against its own patented invention, 'places a substantial hardship' on Jazz, which 'strongly weighs in favor of an injunction.'" D.I. 587 at 11-12. Jazz adds that Avadel "cannot escape an injunction simply because it is smaller than the patentee or because its primary product is an infringing one." *Id.* at 13 (citing *Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1156 (Fed. Cir. 2011)). According to Jazz, Avadel's claims that an injunction would destroy its business are particularly inconsequential, considering the Federal Circuit's resolve that "[o]ne who elects to build a business on a product found to infringe cannot be heard to complain if an injunction against continuing infringement destroys the business so elected." *Windsurfing Intern'l, Inc. v. AMF, Inc.*, 782 F.2d 995, 1003 n. 12 (Fed. Cir. 1986).

Yet, this is not a case where an infringer *elected* to build its business around an infringing product. *See Hynix Semiconductor Inc. v. Rambus Inc.*, 609 F. Supp. 2d 951, 970 (N.D. Cal. 2009) (distinguishing *Windsurfing* where the record proves that the infringement was not willful). Rather, Avadel's investment into Lumryz began in 2019, at a time when "claim 24 of the '782 patent ***did not exist***." D.I. 601 at 17 (emphasis in original); P.I. Tr. 83:20-84:7. While Jazz contends that Avadel "made a 'choice' to focus exclusively on Lumryz," this too was a decision made by Avadel in 2019, and Avadel maintains that it was wholly unaware of Jazz's intent to patent a similar treatment when the decision to prioritize Lumryz was made. Tr. 548:12-13. According to Avadel, when the'782 patent issued in October 2021, Avadel continued to have no knowledge of the patent, but "the design of Lumryz was locked in . . . [and] fully ready for FDA approval." D.I. 601 at 17. Thus, Avadel's alleged harm was not, as Jazz contends, "self-inflicted." D.I. 587 at 1. And "the potential destruction of [] [Avadel's] business

should carry some weight in the balancing of harms under the four-factor test reaffirmed in *eBay*." *See Hynix*, 609 F. Supp. 2d at 970; *see also Wonderland Switzerland AG v. Evenflo Co., Inc.*, No. 1:20-CV-00727-JPM, 2023 WL 4098571, at *7 (D. Del. June 7, 2023) ("[C]ourts may still consider hardships suffered by an infringer when determining whether an injunction is warranted.").

Considering the harm of an injunction to Avadel against the harm to Jazz of allowing Avadel's continued infringement, the Court finds that the balance tilts in Avadel's favor. Avadel is "a much smaller company" that "depends entirely on the sales of the enjoined products for its revenue." *Bio-Rad Lab'ys, Inc. v. 10X Genomics Inc.*, 967 F.3d 1353, 1379 (Fed. Cir. 2020); *but see Commonwealth Sci. & Indus. Rsch. Organisation v. Buffalo Tech. Inc.*, 492 F. Supp. 2d 600, 606 (E.D. Tex. 2007) (finding that hardship of injunction was not catastrophic where the infringing products made up "only eleven percent of [the infringer's] business"). Thus, even the limited injunction sought by Jazz could "[redacted]" Divis Decl., ¶ 6. And while Jazz will undoubtedly suffer harm from having to compete directly against an infringing product, "[Lumryz] is not a copycat product[] but was independently developed and provides important advantages over [Jazz's products] for patients." *Conceptus, Inc. v. Hologic, Inc.*, No. C 09-02280 WHA, 2012 WL 44064, at *3 (N.D. Cal. Jan. 9, 2012). Given this evidence and [redacted],[9] the Court finds that the balance of the equities weighs against an injunction.[10] *Id.* (finding that the

[9]D.I. 601 (explaining that, if an injunction is granted, "[redacted]").

[10]Jazz argues that the balance of the equities should not favor Avadel because "Avadel has purported to have invented other unit dosage forms that would *not* infringe Jazz's claim 24." D.I. 587 at 11. Jazz concedes, however, that "Avadel did not present any evidence of a non-infringing alternative to claim 24 at trial," and Jazz relies on disclosures in Avadel's patent that the "first principal structural embodiment" of Avadel's formulation does not include a viscosity

balance of hardships weighed against an injunction where the infringer "would have to lay off nearly three hundred employees who are directly related to the manufacture and research of [the infringing product] if an injunction is imposed").

4. *Public Interest*

More than any other *eBay* factor, the public interest strongly favors denying Jazz's request to enjoin Lumryz for narcolepsy. "The heart of the patent grant is the right to exclude. *See* 35 U.S.C. § 154(a)(1) ("Every patent shall contain ... a grant to the patentee ... of the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States."). "Typically, in a patent infringement case, although there exists a public interest in protecting rights secured by valid patents, the focus of the district court's public interest analysis should be whether there exists some critical public interest that would be injured by the grant of [injunctive] relief." *Hybritech Inc. v. Abbot Laboratories*, 849 F.3d 1446, 1458 (Fed.Cir.1998); *Wesley Jessen Corp. v. Bausch & Lomb, Inc.*, 209 F. Supp. 2d 348, 404 (D. Del. 2002), *aff'd*, 56 F. App'x 503 (Fed. Cir. 2003) ("In patent cases, courts only exercise their discretion to deny injunctive relief when the harm to the public from granting the injunction is so severe that it outweighs the patentee's individual right to exclude."); *Amgen, Inc. v. Sanofi*, 872 F.3d 1367, 1381 (Fed. Cir. 2017) (holding that where a "plaintiff fails to show 'that the public interest would not be disserved by a permanent injunction,' then the district court may not issue an injunction"). Particularly, "[i]n litigation such as this involving a medical product, the public

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enhancing agent or an acid. *Id.* (noting that Avadel's witness confirmed during trial that "everything in [the '062 Patent] to be true and accurate."). This evidence, however, does not persuade the Court that Avadel had a "new design around [that] was ready for implementation" and does not defeat Avadel's claim that the balance of the harm weighs in its favor. *See Douglas*, 717 F.3d at1345 ("If indeed [defendant] had a non-infringing alternative *which it could easily deliver to the market*, then the balance of hardships would suggest that Buyers should halt infringement and pursue a lawful course of market conduct." (emphasis added)).

has 'two primary interests'—i.e., the 'protection of intellectual-property rights and access to necessary and effective medical care.'" *Abbott*, 2019 WL 2521305, at *25 (quoting *Baxalta*, 2018 WL 3742610, at *12). Thus, courts have denied motions for injunctions "when doing so would eliminate 'an important alternative for patients.'" *Id.* (quoting citation omitted); *see also Custom Designs of Nashville, Inc. v. Alsa Corp.*, 727 F. Supp. 2d 719, 727 (M.D. Tenn. 2010) ("A number of cases indicate that the denial of an injunction for reasons of public interest is limited to cases where public health or safety are threatened, but that in general, the benefits derived from protecting a person's patent sufficiently serve the public interest.").

Avadel contends that a permanent injunction would harm the public interest by removing from the market a treatment for narcolepsy that offers "unique medical benefits" otherwise not offered by Xyrem and Xywav. D.I. 601 at 3. Specifically, Avadel argues that Lumryz constitutes an important alternative for patients with narcolepsy by offering those patients the only single-dose treatment regimen in the market. *Id.* at 4. Xyrem and Xywav, on the other hand, require patients with narcolepsy "to take one dose of oxybate at bedtime and a second dose two and a half to four hours later." Tr. 635:14-22. Avadel's expert, Dr. Corser, testified during trial that Xyrem and Xywav "ha[ve] not been appealing, either for doctors or for patients" because the twice-nightly treatment regimen means that patients must wake up to take the second dose. *Id.* at 635:14-22. Conversely, because Lumryz is only taken once before bedtime, Lumryz "giv[es] narcolepsy patients—for the first time—the chance to get an undisturbed night's sleep." D.I. 601 at 3.

To counter Avadel's argument that Lumryz is the superior treatment, Jazz cites "data show[ing] that both parties' products similarly reduce the number of narcolepsy nighttime awakenings from about 80 to about 40." D.I. 610 at 1; Jazz Exs. 20-22. Yet the data cited by

Jazz does not refute Avadel's claim that Lumryz gives patients with narcolepsy "a better chance to get undisturbed sleep than Jazz's products," as the basis for Avadel's claim is not that Lumryz is more *effective* in *treating* or *preventing* symptoms of narcolepsy. Rather, Avadel argues that, unlike Xywav and Xyrem, Lumryz offers a unique benefit to patients *by eliminating the requirement* that patients take a second late-night dose. D.I. 601 at 4. Accordingly, Avadel claims that an injunction would harm the public interest by preventing patients with narcolepsy from accessing a treatment that is easier to administer. Stern Decl., ¶¶ 6-8

Notably, the FDA similarly found that Lumryz 's single dose regimen treatment made it clinically superior "to every previously approved oxybate drug . . . , [including] both Xywav and Xyrem," for patients with narcolepsy. Avadel Ex. 1 at JTX-112.3. The FDA's determination relied on the opinions of "agency sleep experts" who agreed that "disrupting sleep contributes to chronic sleep loss[] [and] is well known to cause reduced performance, increased risk for accidents and death, and detrimental effects on both psychological and physical health." *Id.* at JTX-0112.3, JTX-112.33. Thus, the FDA found that a treatment for narcolepsy that required patients "to wake up to take a second dose" would be "antithetical to [the treatment's] goal of improving sleep" because it would force a nocturnal arousal on patients who already struggle to get sufficient night-time sleep. *Id.* at JTX-112.29. Because Lumryz eliminated the need for patients with narcolepsy to wake up for the second dose, the FDA concluded that Lumryz was "inherently more convenient, easier, and less burdensome," and thus was the superior treatment for narcolepsy.[11] *Id.* at JTX-112.30.

[11] Jazz contends that "[t]he FDA found that Xywav's significantly lower amount of sodium is 'safer' for 'all patients with narcolepsy.'" D.I. 587 at 9. Jazz, however, mischaracterizes the FDA's findings, which were "not based on Lumryz providing greater safety than Xyrem and Xywav" and did "not respond[] to each safety argument from Jazz." Avadel Ex. 1 at JTX-

Jazz contends that "the FDA made clear that its finding was not based on better safety or efficacy." D.I. 587 at 15. While the Court agrees that the FDA did not determine whether Lumryz was a safer or more effective treatment for narcolepsy, Avadel can show that its infringing product constitutes an important alternative for patients even in the absence of such evidence. *Baxalta* is illustrative. 2018 WL 3742610. There, the district court found that a Breakthrough Therapy designation by the FDA "indicate[d] that the [infringing] drug may demonstrate a substantial improvement over existing therapies" where the patentee sought to enjoin the sale and production of an infringing drug used to treat hemophilia. *Id.* at *3. In denying injunctive relief, the *Baxalta* court noted that the infringing drug was administered through "a once-weekly subcutaneous injection" while the patented treatment required administration by infusion "at least two times a week." *Id.* Identifying this difference in the administration requirements of each treatment, the *Baxalta* court held that the infringing product "represent[ed] a potential sea change in the treatment of [] hemophilia" because it offered patients an option for "prophylactic therapy with *a significantly lower treatment burden*." *Id.* at

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0112.34. Acknowledging "that the sodium content of Lumryz raises [] [some] safety concern[s]," particularly for patients with sensitivity to sodium, the FDA determined that, with respect to both patients with sodium restrictions and patients who are not sensitive to sodium, "the benefit offered by once-nightly dosing would [still] outweigh the risk of increased sodium intake." *Id.* at JTX-0112.33; *id.* at JTX-0112.34 (noting that the FDA "acknowledged [] that Lumryz has a higher sodium content than Xywav and addressed why Lumryz is still clinically superior to Xywav"). Thus, the Court does not read the FDA's superiority determination as applying only to patients with no salt-sensitivity. *Compare* D.I. 587 at 16 (claiming that the FDA's "clinical superiority finding was not for 'the entire patient population for which [Lumryz] is intended'") *with* Avadel Ex. 1 at JTX-0112.32 ("[W]e believe that the benefit of Lumryz's once-nightly dosing outweighs the safety concern raised by its increased sodium content for a substantial number of narcolepsy patients.") *and* Avadel Ex. 1 at JTX-0112.33 ("For certain sodium-sensitive patients with narcolepsy, the benefit offered by once-nightly dosing would outweigh the risk of increased sodium intake . . . .").

*13 (emphasis added). Thus, "the public interest favor[ed] availability of [this less burdensome] treatment." *Id.*

Similarly, in this matter, the FDA's superiority determination strongly indicates that the public interest favors the availability of Lumryz for narcolepsy. As with the infringing treatment in *Baxalta*, Lumryz's single-dose treatment regimen benefits patients with narcolepsy by eliminating the need to "wak[e] up to take medication during the night after falling asleep[]." Avadel Ex. 1 at JTX-0112.12. The FDA explained that this benefit can be crucial for patients with narcolepsy, since "even [] a single nocturnal arousal[] [] can [cause] impairment of alertness and decline in cognitive performance the following day." *See id.* at JTX-01112.29 ("Awakening to take a second dose necessarily disrupts sleep and causes fragmented sleep. A person with disrupted sleep cannot simply return to sleep and resume their normal sleep cycle. . . . So, upon taking a second dose of Xyrem or Xywav, after the minimum of 5-15 minutes to return to sleep, such sleep does not resume where the patient left off to take their medication."). A single-dose treatment regimen, on the other hand, aligns more effectively with the goal of narcolepsy treatment (i.e., "maximize the time in sleep and minimize wake time") by eliminating the need to wake mid-sleep for a second dose. *Id.* Such a treatment also reduces the burden on patients of having to arrange for such a late-night dose. *Id.*; Stern Decl., ¶¶ 7-8 (noting "[t]hat patients taking Xyrem or Xywav must set an alarm to take the second dose in the middle of the night" makes compliance less likely, as "patients [] struggle[] to adhere to the dosing regimen"); Lavender Decl., ¶ 12 ("[I]t is not some minor issue that people do not want to have to set an alarm in the middle of the night. Neither Xyrem nor Xywav is an easy treatment. The treatment upends your life."). Thus, Avadel has proven that Lumryz represents a "sea change" in the treatment of narcolepsy by offering patients a less burdensome treatment option.

In light of this evidence, the public interest weighs notably against even the "limited" injunction sought by Jazz. Lumryz is the only single-dose treatment for narcolepsy, and the FDA's superiority determination recognized that Lumryz is "significantly more convenient for patients" and "an advancement in the ease of drug administration." Avadel Ex. 1 at JTX-01112.29. Avadel offered first-hand accounts from patients and providers noting their preference for Lumryz's once-nightly treatment regimen over Jazz's two-dose oxybate treatments. *See, e.g.*, Lavender Decl., ¶¶ 12-17; Patient 1 Decl., ¶¶ 6-11; Patient 2 Decl., ¶¶ 6-10. While Jazz contends that a limited injunction reduces the likelihood of public harm by ensuring that no existing Lumryz patients are enjoined from continuing their use of Lumryz, Jazz seeks an injunction that "would make Lumryz unavailable 'to the vast majority of [narcolepsy] patients in need of [Lumryz] treatment.'" D.I. 601 at 10 (citing *Baxalta*, 2018 WL 3742610, at *13). In doing so, Jazz ignores that patients with narcolepsy who have not been prescribed Lumryz would also "continue to benefit[] from having a choice of products."[12] *Conceptus*, 2012 WL 44064, at *3-*4; *see also Baxalta*, 2018 WL 3742610, at *12 (explaining that the public interest disfavored enjoining a treatment that "differ[s] in meaningful ways" from other existing products on the market). In fact, there are "multiple reasons patients may want to take Lumryz in the future but are not taking it yet." Stern Decl., ¶ 21. As Avadel's expert Dr. Thomas Stern explained:

[12]The Court recognizes that some patients may benefit more from Xywav given its reduced sodium content. However, the FDA found "that the benefit of Lumryz's one-nightly dosing outweighs the safety concern raised by its increased sodium content for a substantial number of narcolepsy market." Avadel Ex. 1 at JTX-0112.32. While Jazz disagrees and notes that has initiated proceedings to challenge the FDA's determination on this ground, the public interest that the Court seeks to protect is the interest in patient choice, and the Court's decision ensures that all patients seeking narcolepsy treatment have the option to take a treatment that offers unique and substantial benefits. The law does not require the Court to find that Lumryz *is* the best treatment option for all patients with narcolepsy.

> Some [patients] have not yet been diagnosed with narcolepsy. Others have been diagnosed with narcolepsy and would benefit from Lumryz but have not started taking it because they have not had a follow-up visit recently or have not yet gone through the somewhat cumbersome process of enrolling in the FDA-mandated risk evaluation and mitigation system (REMS) for Lumryz or securing coverage from their health insurer. Some are not yet 18 years of age. *Id.*

Jazz responds that these patients can be treated with Jazz's oxybate products. *See* D.I. 597 at 14 (citing JTX87.3) (noting "that Lumryz's labeling instructs that Jazz's patients are to switch to 'the nearest equivalent [Lumryz] dosage in grams per night.'"). Yet, Jazz does not offer a once-nightly treatment for narcolepsy, and the record does not indicate that Jazz intends to offer a once-nightly narcolepsy treatment "for commercial sale very soon." *Edwards Lifesciences AG v. CoreValve, Inc.*, No. CV 08-91 (GMS), 2014 WL 1493187 (D. Del. Apr. 15, 2014) (excluding from an injunction those patients who "cannot be helped" by the patentee's products). Thus, with respect to their administration requirements, Jazz's oxybate treatments and Lumryz "are 'not interchangeable products." *Abbott*, 2019 WL 2521305, at *27 (internal citations omitted). Given the detrimental effects of sleep deprivation and sleep fragmentation for patients with narcolepsy, it is in the public's interest to have continued access to the less burdensome treatment. Avadel Ex. 1 at JTX-01112.13. Moreover, this interest in protecting patient access to the only once-nightly narcolepsy treatment in the narcolepsy market "'militates strongly against an injunction.'" *Abbott*, 2019 WL 2521305, at *26-*27 (internal citations omitted); *Conceptus*, 2012 WL 44064, at *4 (N.D. Cal. Jan. 9, 2012).

In sum, having considered each of the *eBay* factors, the Court finds the threat to Avadel's business and, more importantly, the substantial harm to the public interest that would result from an injunction outweigh any irreparable injury suffered by Jazz in the absence of such injunctive relief. Accordingly, Jazz's request for a permanent injunction barring the prescription of Lumryz for the treatment of narcolepsy is **DENIED**.

B. *The eBay factors weigh in favor of enjoining Avadel from seeking FDA approval and marketing Lumryz for IH.*

1. *Irreparable Harm*

According to Jazz, Lumryz's entrance into the market for IH would irreversibly harm Jazz's market share and damage its ability to build its reputation as the exclusive market leader. D.I. 587 at 4-5, 7-8. For the following reasons, the Court agrees that Jazz would suffer irreparable injury if Avadel is not enjoined from seeking FDA approval and marketing Lumryz for IH.

Unlike the narcolepsy market where Jazz's products compete with several other oxybate therapies, Jazz's Xywav is the only FDA-approved treatment for IH. Tr. 92:17-21, 520:5-8. While Avadel does not currently manufacture or sell competing products in the IH market, Avadel does not dispute that it is pursuing FDA approval of Lumryz for the treatment of IH. Tr. 519:17-19. The evidence shows that Avadel's interest in the IH market stems from its recognition that the market holds "a lot of opportunity" because "there's a robust patient population . . . with only one currently FDA approved treatment, [Xywav]." Jazz Ex. 2 at 23. Because Xywav is the only FDA approved treatment for IH, Lumryz's entrance into the IH market would undoubtedly cause Jazz to suffer significant injury.

Indeed, with FDA approval, Lumryz will compete head-to-head against Xywav in a newly-developing market. *Douglas,* 717 F.3d at 1345 ("Where two companies are in competition against one another, the patentee suffers the harm—often irreparable—of being forced to compete against products that incorporate and infringe its own patented inventions."). Avadel responds that Jazz's complaints about "losing its first-mover advantage are overstated." D.I. 601 at 4 (internal citations omitted). Yet, evidence shows that, since acquiring FDA approval to market Xywav for IH in August 2021, Jazz has seen dramatic increases in the

number of IH patients taking Xywav year-to-year. P.I. Tr. 16:7-10, 17:12-19 (noting a 59% growth of Xywav for IH in 2023). Additionally, as recently as March 2024, Avadel's CEO admitted that Avadel "watched [Xywav] advance" over the two years since their launch in the IH market and noted "a lot of opportunity remained" because Jazz showed less than a ten percent market penetration. Jazz Ex. 2 at 23:10-21.

Given this evidence, the Court agrees that an encroachment by Avadel at such a "crucial inflection point" in the development of the IH market would harm Jazz by allowing Avadel to "capture and define the market with pirated technology." *Illumina, Inc. v. Qiagen, N.V.*, 207 F. Supp. 3d 1081, 1093 (N.D. Cal. 2016). "[A]s the first entrant into the marketplace, [Avadel] would have advantages that include working with the best facilities and potential customers and being perceived as an innovator in the field." *See Butamax Advanced Biofuels LLC v. Gevo, Inc.*, 868 F. Supp. 2d 359, 375 (D. Del.), *remanded-in-part on other grounds. Butamax(TM) Advanced Biofuels LLC v. Gevo, Inc.*, 486 F. App'x 883 (Fed. Cir. 2012); *see also Purdue Pharma L.P. v. Boehringer Ingelheim GMBH*, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (finding irreparable harm where "price erosion and loss of market position was likely").

Moreover, Xywav's title as the only FDA-approved treatment for IH "is an intangible asset that is part of a company's reputation . . . ." *Douglas*, 717 F.3d at 1345. Because Jazz intends to use its exclusivity in the IH market to brand itself as the market leader, Avadel's entrance into the market would strip Jazz of a unique selling point critical to growing its reputation and goodwill. *See id.* at 1344 (recognizing that a patented product may "lose some of its distinctiveness and market lure because competitors could contend that they had 'similar features' without noting that those features infringe"). Thus, Jazz would also suffer reputational harm from "being precluded from marketing to potential and existing customers that it is the

exclusive market leader." *Celsis In Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 930-31 (Fed. Cir. 2012). This reputational harm and the accompanying market share loss caused by Avadel's direct competition would likely be irreparable. *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms. Inc.*, 821 F. Supp. 2d 681, 694 (D.N.J. 2011), *aff'd and remanded sub nom. Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms. Inc., USA*, 748 F.3d 1354 (Fed. Cir. 2014) (finding irreparable harm where "[p]laintiffs and [d]efendants are two head -to-head competitors in the [relevant] marketplace; every sale of [d]efendants' generic [product] is a lost sale by Plaintiff"). Accordingly, this factor weighs in favor of a permanent injunction.[13]

2. *Inadequacy of Legal Remedies*

Additionally, Jazz has satisfied its burden of showing that monetary remedies would not adequately compensate the harm caused by Lumryz's introduction into the market for IH. This factor can be met by evidence of "loss of market share, brand recognition, and customer goodwill . . . particularly when the infringing acts significantly change the relevant market." *i4i*, 598 F.3d at 862. Here, the approval of Lumryz for IH would significantly change the market by allowing a second treatment to compete directly with Jazz's Xywav. *See Novozymes A/S v. Genencor Int'l, Inc.*, 474 F. Supp. 2d 592, 613 (D. Del. 2007) (finding legal remedies inadequate because patentee and infringer "are head-to-head competitors, and [patentee] has a right, granted by Congress, not to assist its rival with the use of proprietary technology"). Also, as the Court noted *supra*, Jazz's exclusivity in the IH market is itself an intangible asset, and Jazz will likely suffer reputational harm that cannot be compensated by legal remedies. *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1340 (Fed. Cir. 2012) ("Loss of business

[13]For the same reasons noted with respect to Jazz's request to enjoin Lumryz for narcolepsy, Jazz has shown a sufficient nexus between the irreparable harm asserted by Jazz and Avadel's continued infringement. *See supra* at 8-10.

opportunity or damage to brand recognition could provide a basis for concluding that monetary relief would be inadequate.").

3. *Balance of the Equities*

The balance of the equities also tips in Jazz's favor. While the Court is persuaded that enjoining Lumryz for narcolepsy would irrevocably harm Avadel's business, Avadel cannot allege the same injury with respect to the IH market, where Avadel still lacks FDA approval to sell Lumryz. And while Avadel notes that it "intends to invest $30-40 million" in clinical trials evaluating the contributions of Lumryz in treating IH, Avadel concedes that it "has not yet started [any] clinical trial[s]" and would not do so if an injunction was granted. *See* P.I. Tr. 64:15-21, 86:1-8 (explaining that the trials would not occur "if there was no way that it could sell the product at the conclusion of that clinical trial."). Thus, enjoining Lumryz for IH would not spell "the end of Avadel." *See* D.I. 601 at 17.

"On the other hand, requiring [Jazz] to compete against its own patented invention . . . places a substantial hardship on [Jazz]," particularly given that Lumryz would be the only other FDA-approved treatment for IH. *Robert Bosch*, 659 F.3d at 1156; *see also* Jazz Ex. 2 at 23 (Avadel's CEO recognizing "a lot of opportunity" in the IH market). Jazz contends that it is working to grow its position and reputation in the IH market and, as the Court noted above, Jazz has a pointed interest in protecting its market exclusivity. This factor therefore weighs in favor of a permanent injunction.

4. *Public Interest*

Avadel contends that the same public interest considerations that counsel against enjoining Lumryz for narcolepsy are relevant to Jazz's request to enjoin Lumryz for IH. D.I. 601

at 9-10. For the following reasons, the Court disagrees and finds that the public interest weighs in favor of enjoining Lumryz in the IH market.

According to Avadel, "IH is best thought of as being on a spectrum with narcolepsy," as "[p]atients with either condition suffer from excessive daytime sleepiness," "[d]iagnostic criteria are similar and imprecise," and "oxybate is a very effective treatment for IH." *Id.* at 9. While the Court agrees that both narcolepsy and IH are sleep-related disorders that share many common symptoms, the weight of the evidence indicates that the conditions are distinguishable. Jazz's expert witness, Dr. Richard K. Bogan, explained that "Narcolepsy and IH are two unique chronic sleep disorders with the common symptom of excessive daytime sleepiness ('EDS')." Bogan Decl., ¶ 10. While both conditions cause patients to suffer EDS, "IH patients[] [] present other symptoms that are typically distinct from narcolepsy." *Id.*, ¶ 14. These symptoms include "sleep inertia where the patient experiences difficulty waking from a long sleep, unrefreshing naps, and long sleep times of 11 or more hours per 24-hour period." *Id.*

Avadel's expert, on the other hand, alleged that IH was particularly similar in "presentation and diagnostic criteria to [Narcolepsy Type 2]," making the two conditions "difficult to distinguish." Stern Decl., ¶ 14. While Dr. Bogan agreed that IH and narcolepsy Type 2 have many "overlapping symptoms," he explained that Type 2 tends to cause patients to suffer from fragmented sleep. Bogan Decl., ¶ 12. Patients with IH, on the other hand, "typically have longer sleep times." *Id.* Thus, Dr. Bogan testified that practitioners can distinguish between the two conditions. *Id.* Dr. Bogan supported his opinions with several peer-review papers "consistently characterize[ing] IH and narcolepsy [] as distinct diseases." *Id.* at Ex. C, Dauvilliers 2022 at 7 (explaining that IH "may coexist with other disorders. . . but is incompatible with others, such as narcolepsy"); Ex. D, Landzberg, D and Trotti, L.M., *Is*

Idiopathic Hypersomnia a Circadian Rhythm Disorder?, Curr. Sleep. Med. Rep. 5(4):201-206 (2019) ("IH is diagnosed based on clinical history in combination with objective quantification of excessive daytime somnolence . . . after excluding other causes of sleepiness such as narcolepsy type 1 [and] narcolepsy type 2"). Several of these papers distinguished IH "from narcolepsy on the basis of the presence of prolonged rather than short diurnal sleep periods . . . ." *Id.* at Ex. E, Bruck, D. and Parkes, J.D., *A comparison of idiopathic hypersomnia and narcolepsy-cataplexy using self report measures and sleep diary data*, JNNP 60:576-578 (1996); Ex. F, Manfredi, R.L., et al., *Disorders of excessive sleepiness: narcolepsy and hypersomnia*, Semin. Neurol. 7(3):250-58 (1987) ("Nocturnal sleep is typically disrupted in narcolepsy, whereas in idiopathic hypersomnia it is prolonged."). During a conference presentation in March 2024, Avadel's CEO similarly recognized that IH is "different from narcolepsy in that [IH patients] really physically struggle at times with waking up with the deep sleep inertia that they suffer from." Jazz Ex. 2 at 23:10-24:1.

The separate FDA-labeled-indications for IH and narcolepsy also support the Court's finding that the two conditions are distinct. For instance, Xywav is FDA-approved for once nightly administration to treat IH and must be administered in two doses to treat narcolepsy. Citing only to the declaration of its expert, Dr. Stern, however, Avadel argues that the Court should disregard the FDA's approval of once nightly Xywav to treat IH because a "vast majority of IH patients take [Xywav] twice nightly." D.I. 601 at 8 (citing Stern Decl., ¶ 16). Yet, Avadel provided no evidence to substantiate Dr. Stern's claim. *See* Stern Decl., ¶ 16 (noting only that, "in [his] own practice, [Dr. Stern] always starts patients on twice-nightly oxybate for IH"). Jazz, on the other hand, cited clinical research finding no substantial difference between once nightly dosing and twice nightly dosing of Xywav for IH treatment. *See* Jazz Ex. 26 at 63. When

viewed as a whole, the weight of the evidence shows that IH and narcolepsy are distinct conditions and that Xywav can—and very likely is—administered in a single dose to treat the symptoms of IH.

Given these distinctions between the two conditions, Avadel cannot rely on the FDA's determination that "Lumryz is clinically superior to Xywav" to support its claim that the public interest weighs against the injunction of Lumryz for IH. Indeed, the FDA's superiority determination extends only to the narcolepsy market. Avadel responds that the Court's decision to enjoin Lumryz for IH should not turn on its lack of FDA approval because "[t]he key public-interest consideration is whether an injunction would cut off patient access to a differentiated product that offers a 'unique' medical benefit, not whether there has been a clinical superiority determination." D.I. 601 at 9. While the Court agrees that the public interest may disfavor an injunction even in the absence of an FDA superiority finding, in this case, the FDA's ODE determination was crucial to the Court's finding that Lumryz offered a "unique" medical benefit to patients with narcolepsy. *See supra* at 15-21. In opposing an injunction of Lumryz™ for narcolepsy, Avadel argued consistently with the FDA that Lumryz was the superior treatment because it eliminated the need for narcolepsy patients to wake for a late-night second dose. *See* D.I. 609 at 4-5. After reviewing the FDA's ODE determination and the evidence before it, the Court agreed that the public had a significant interest in accessing the only single-dose treatment for narcolepsy. *See supra* at 15-21. Given the FDA's approval of once-nightly Xywav as a safe and effective treatment for IH, however, the Court is not persuaded that Lumryz offers IH patients the same "unique" benefit. As Avadel has not shown that Lumryz offers any other distinct benefits to patients with IH, the Court cannot find that enjoining Lumryz for IH would harm the public interest by "cutting off" access to a differentiated product.

Ultimately, to show that the public interest weighed against an injunction, Avadel had the burden to prove that enjoining Lumryz for IH would result in a harm to the public that outweighs the public's competing interest in incentivizing "innovative drug companies to continue costly development efforts." *Sanofi-Synthelabo*, 470 F.3d at 1383 (finding that the "'public interest in encouraging investment in drug development and protecting the exclusionary rights conveyed in valid pharmaceutical patents' tips the scale in [the patentee's] favor"). Yet, Avadel failed to show that Lumryz is a superior or unique treatment for IH. Avadel's claim that "[p]hysicians have [] urged Avadel to seek FDA approval for Lumryz in IH" is similarly insufficient to outweigh the public's interest in enforcing patent rights and encouraging innovation. *See* D.I. 601 at 8. Accordingly, this factor weighs in favor of enjoining Lumryz for IH.

5. *Unclean Hands*

Avadel contends that Jazz cannot obtain equitable relief because of Jazz's attempts to use "unlawful and improper means" to block Avadel's participation in the marketplace. D.I. 601 at 18. Federal Rule of Civil Procedure 8(c), however, requires the affirmative defense of unclean hands to be pled affirmatively, and "[f]ailure to raise an affirmative defense by responsive pleading or by appropriate motion generally results in the waiver of that defense." *Charpentier v. Godsil*, 937 F.2d 859, 863 (3d Cir.1991). Because Avadel failed to plead unclean hands, that defense is waived. D.I. 610 at 5. Moreover, the defense would not succeed even if properly pled by Avadel given that "the primary principle guiding application of the unclean hands doctrine is that the alleged inequitable conduct must be connected, *i.e.,* have a relationship, to the matters before the court for resolution." *In Re New Valley Corp.,* 181 F.3d 517, 525 (3d Cir.1999) (internal citations omitted). "In the context of patent litigation, assertions of unclean hands have typically succeeded only in situations in which the misconduct related in some way to the

procurement of the particular patent in question." *In re Gabapentin Pat. Litig.*, 648 F. Supp. 2d 641, 650 (D.N.J. 2009). Jazz's exclusion of Avadel from the marketplace does not directly relate to Jazz's claim asserting its patent rights. Accordingly, the defense, even if properly pled, would not bar Jazz from seeking an injunction.

Because the *eBay* factors counsel in favor of an injunction, Jazz's request to enjoin Avadel from pursuing FDA approval for Lumryz to treat IH and from marketing Lumryz for IH treatment is **GRANTED**.

2. Ongoing Royalties

A. *Jazz is entitled to ongoing royalties for sales of Lumryz for narcolepsy.*

"If the court determines that a conduct-barring injunction is not warranted, it may instruct the parties to try to negotiate an ongoing royalty and, if the parties cannot agree, award a royalty." *Prism Techs. LLC v. Sprint Spectrum L.P.*, 849 F.3d 1360, 1377 (Fed. Cir. 2017). While the jury awarded Jazz a 3.5% royalty rate for past damages, Jazz argues that the awarded royalty should be increased to an ongoing rate of "27% through 2025, 13% from 2026 through 2032, and 3.5% from 2033 through February 2036." D.I. 587 at 17-18. Avadel, on the other hand, requests that the Court "view the jury award as a fully-paid-up royalty" or, alternatively, "treat the award as a determination that Avadel should pay a 3.5% royalty on 20% of Avadel sales." D.I. 601 at 19.

Although the Court recognizes that the award of an ongoing royalty is not automatic, the Court agrees with Jazz that an award of royalties is warranted to remedy the future sales of Lumryz for narcolepsy. The decision to award such a royalty is solely within the Court's discretion. *See Paice LLC v. Toyota Motor Corp.,* 504 F.3d 1293, 1315 (Fed.Cir.2007). Moreover, "the Federal Circuit has indicated that a prevailing patentee should receive

compensation for any continuing infringement." *Apple, Inc. v. Samsung Elecs. Co.*, No. 12-00630-LHK, 2014 WL 6687122, at *7 (N.D. Cal. Nov. 25, 2014) (citing *Telcordia Techs., Inc. v. Cisco Sys., Inc.*, 612 F.3d 1365, 1379 (Fed.Cir.2010)). Here, the record clearly establishes that Avadel intends to offer and sell a wholly infringing product to treat narcolepsy. The evidence also shows that Avadel recognizes that its product will compete directly with Jazz's oxybate products for market share and other market opportunities. As some evidence indicates that Avadel has and continues to target patients currently being treated by Xyrem or Xywav (i.e., so-called "switch-patients"), the Court agrees that an ongoing royalty award is necessary to compensate for Avadel's continuing infringement of the '782 patent. Avadel's motion for ongoing royalties is therefore granted.

B. *Additional testimony is necessary to determine the proper rate.*

In determining the appropriate ongoing royalty rate, the Court must consider: (1) change in bargaining position; (2) changed economic circumstances; and (3) any post-verdict factors affecting a post-verdict hypothetical negotiation. *See Vectura Ltd. v. GlaxoSmithKline LLC*, No. CV 16-638-RGA, 2019 WL 4346502, at *7 (D. Del. Sept. 12, 2019). "Generally, the jury's damages award is a starting point for evaluating ongoing royalties." *Apple, Inc.*, 2014 WL 6687122, at *14. Courts have increased the jury's royalty rate for ongoing infringement where "there was evidence of changed economic circumstances, in addition to the patentee being in a stronger bargaining position." *Purewick Corp. v. Sage Prod., LLC*, 666 F. Supp. 3d 419, 449 (D. Del. 2023), *appeal dismissed*, No. 2023-1868, 2023 WL 4230367 (Fed. Cir. June 28, 2023), *and appeal dismissed*, No. 2024-1184, 2024 WL 889332 (Fed. Cir. Mar. 1, 2024).

Here, given Jazz's status as the prevailing party, the Court agrees that Jazz is in a stronger bargaining position. *Amado v. Microsoft Corp.*, 517 F.3d 1353, 1361 (Fed.Cir.2008) ("There is a

fundamental difference [] between a reasonable royalty for pre-verdict infringement and damages for post-verdict infringement.") (internal citations omitted).[14] Yet, the parties submitted limited briefing on any economic factors or post-verdict factors for the Court to consider in determining the appropriate ongoing rate. Also, given that Jazz was the only party to present testimony from a damages expert during trial, the Court finds that additional briefing and evidence is necessary to determine the extent to which Jazz's bargaining position and changes in the economic circumstances justify an increase in the rate awarded by the jury.[15] Accordingly, while the Court agrees that Jazz may be entitled to ongoing royalties at a rate greater than the 3.5% rate awarded by the jury, the Court will reserve judgment on the appropriate ongoing royalty rate to compensate Jazz for Avadel's future infringement in the narcolepsy market, pending additional briefing from the parties.

III. CONCLUSION

For the foregoing reasons, the Court **GRANTS-IN-PART** and **DENIES-IN-PART** Plaintiffs Jazz Pharmaceuticals Inc. and Jazz Pharmaceuticals Ireland Limited's Motion for a Permanent Injunction and for an Ongoing Royalty (D.I. 586). An appropriate Order will follow.

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[14]Indeed, "[p]rior to judgment, liability for infringement, as well as the validity of the patent, is uncertain, and damages are determined in the context of that uncertainty. Once a judgment of validity and infringement has been entered, however, the calculus is markedly different because different economic factors are involved." *Amado,* 517 F.3d at 1362. Accordingly, "[a]n assessment of prospective damages for ongoing infringement should 'take into account the change in the parties' bargaining positions, and the resulting change in economic circumstances, resulting from the determination of liability.'" *ActiveVideo*, 694 F.3d at 1343 (internal citations omitted).

[15]In deciding the royalty rate for post-trial infringement, the Court may consider "any new evidence that was not before the jury and additionally any changed circumstances (other than willfulness) between a hypothetical negotiation that occurred . . . (which the jury determined) and a hypothetical negotiation that would occur [now] after the judgment." *Mondis Tech. Ltd. v. Chimei InnoLux Corp.*, 822 F. Supp. 2d 639, 647 (E.D. Tex. 2011), *aff'd sub nom. Mondis Tech. Ltd. v. Innolux Corp.*, 530 Fed.Appx. 959 (Fed. Cir. 2013).

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS LLC, Defendant.	C.A. No. 21-691-GBW
JAZZ PHARMACEUTICALS, INC. and JAZZ PHARMACEUTICALS IRELAND LIMITED, Plaintiff, v. AVADEL CNS PHARMACEUTICALS LLC, Defendants.	C.A. No. 21-1138-GBW
JAZZ PHARMACEUTICALS, INC. and JAZZ PHARMACEUTICALS IRELAND LIMITED, Plaintiff, v. AVADEL CNS PHARMACEUTICALS LLC, Defendants.	C.A. No. 21-1594-GBW

ORDER

At Wilmington this 27th day of August 2024, **IT IS HEREBY ORDERED** that Plaintiffs Jazz Pharmaceuticals Inc. and Jazz Pharmaceuticals Ireland Limited's (collectively, "Jazz") Motion for a Permanent Injunction and for an Ongoing Royalty (D.I. 586) against Defendant Avadel CNS Pharmaceuticals LLC ("Avadel") is **GRANTED-IN-PART** and **DENIED-IN-PART** as follows:

1. Jazz's motion for a limited permanent injunction prohibiting Avadel from seeking approval from the U.S. Food and Drug Administration ("FDA") and marketing Lumryz for the treatment of IH is **GRANTED**, and Avadel and each of its officers, servants, employees, attorneys, and any other persons who are in active concert or participation with them, are hereby permanently enjoined from infringing in any way Claim 24 of the '782 patent, by making, using, or selling Lumryz or any product not more than colorably different from Lumryz, through and including the expiration date of the '782 patent, including any U.S. Patent Office extensions granted thereon.

    A. Excluded from this injunction are making, using, and selling Lumryz: (a) for the treatment of narcolepsy; (b) for the patients who have been prescribed Lumryz as of the effective date of the injunction conditional on Avadel paying appropriate renumeration to be determined; (c) in currently-ongoing clinical trials and studies; (d) to update data in old studies if necessary; and (e) to re-run necessary tests for quality control for regulators or customers.

B. For the avoidance of doubt, for the duration of this injunction, while Avadel may continue to use Lumryz in currently-ongoing clinical trials and studies pursuant to paragraph 1(A) above, Avadel may not seek approval of Lumryz from the FDA for the treatment of IH or for any indication that was not already part of Lumryz's approved product labeling as of March 4, 2024.

2. Jazz's motion for an ongoing royalty from Avadel to compensate Jazz for any future sale of infringing products to patients with narcolepsy is **GRANTED**, pending additional briefing on the appropriate ongoing rate above 3.5%. Each party may file an opening letter brief not to exceed seven (7) pages on or before Monday, September 16, 2024, at 5:00 pm, outlining their position on the appropriate ongoing royalty rate, which may include any evidence that was not before the jury and additionally any changed circumstances that support their respective positions. Each party may submit an answering letter brief not to exceed four (4) pages on or before Monday September 23, 2024, at 5:00 pm.

3. The undersigned expressly retains jurisdiction to enforce the judgment and permanent injunction pertaining to this action.

GREGORY B. WILLIAMS
UNITED STATES DISTRICT JUDGE

CONFIDENTIAL MATERIAL OMITTED

CONFIDENTIAL PURSUANT TO
PROTECTIVE ORDERS (ECF Nos. 96, 309, 361, 425)

Appx38-44

(12) **United States Patent**
Allphin et al.

(10) **Patent No.: US 11,147,782 B1**
(45) **Date of Patent: Oct. 19, 2021**

(54) **GHB FORMULATION AND METHOD FOR ITS MANUFACTURE**

(71) Applicant: **JAZZ PHARMACEUTICALS IRELAND LIMITED**, Dublin (IE)

(72) Inventors: **Clark Allphin**, Seattle, WA (US); **Scott Bura**, Gilroy, CA (US)

(73) Assignee: **JAZZ PHARMACEUTICALS IRELAND LIMITED**, Dublin (IE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/210,064**

(22) Filed: **Mar. 23, 2021**

Related U.S. Application Data

(63) Continuation of application No. 17/118,041, filed on Dec. 10, 2020, now Pat. No. 11,077,079, which is a continuation of application No. 16/448,598, filed on Jun. 21, 2019, now abandoned, which is a continuation of application No. 15/047,586, filed on Feb. 18, 2016, now Pat. No. 10,398,662.

(60) Provisional application No. 62/117,889, filed on Feb. 18, 2015.

(51) **Int. Cl.**

A61K 31/19	(2006.01)
A61K 9/50	(2006.01)
A61K 31/785	(2006.01)
A61K 38/02	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/19*** (2013.01); ***A61K 9/5031*** (2013.01); ***A61K 31/785*** (2013.01); ***A61K 38/02*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/19; A61K 31/785; A61K 38/02; A61K 9/5031
See application file for complete search history.

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(57) **ABSTRACT**

The present application relates to GHB formulations and methods for manufacturing the same.

24 Claims, No Drawings

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GHB FORMULATION AND METHOD FOR ITS MANUFACTURE

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. application Ser. No. 17/118,041, filed Dec. 10, 2020, which is a continuation of U.S. application Ser. No. 16/448,598, filed Jun. 21, 2019, which is a continuation of U.S. application Ser. No. 15/047,586, filed Feb. 18, 2016 (now U.S. Pat. No. 10,398,662), which claims priority to U.S. Provisional Application Ser. No. 62/117,889, filed Feb. 18, 2015, the disclosures of which are herein incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

Gamma-hydroxybutyrate (GHB), also known as "oxybate," is an endogenous compound with hypnotic properties that is found in many human body tissues. GHB is present, for example, in the mammalian brain and other tissues. In the brain, the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (See Snead and Morley, 1981, Brain Res. 227(4): 579-89). The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e., daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency, reduces sleep apnea, and improves general anesthesia (see, e.g., U.S. Pat. Nos. 6,472,431; 6,780,889; 7,262,219; 7,851,506; 8,263,650; and 8,324,275; each of which is incorporated herein by reference in its entirety).

Sodium oxybate (Na.GHB), commercially sold as Xyrem®, is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. It can be used for other sleep time disturbances. Na.GHB has also been reported to be effective for relieving pain and improving function in patients with fibromyalgia syndrome (See Scharf et al., 2003, J. Rheumatol. 30: 1070; Russell et al., 2009, Arthritis. Rheum. 60: 299), and in alleviating excessive daytime sleepiness and fatigue in patients with Parkinson's disease, improving myoclonus and essential tremor, and reducing tardive dyskinesia and bipolar disorder (See Ondo et al., 2008, Arch. Neural. 65: 1337; Frucht et al., 2005, Neurology 65: 1967; Berner, 2008, J. Clin. Psychiatry 69: 862).

SUMMARY OF THE INVENTION

GHB has a short in vivo half-life, so various embodiments of the invention include a formulation and a method for manufacturing a GHB formulation. One embodiment of the invention is a GHB formulation comprising polymeric beads and pharmaceuticals acceptable excipients. The formulation can be a solid or a liquid. Additional agents, such as surfactants, may be added to control the release of GHB from within the polymeric bead, such as sodium lauryl sulfate or stearic acid. The beads can be coated with a flexible film. Optionally, the formulation can contain supplemental anions separate from the coated or uncoated resin particles to facilitate exchange of the GHB when natural (e.g., physiologically produced) anions in the gut are depleted.

In another embodiment of the invention, a precursor to GHB, called gamma butyrolactone (GBL) is loaded onto a hydroxide form Type 1 strong base anion resin (or its equivalent) and the GBL is converted to GHB in the bead to form a GHB resinate product. One can achieve high loading efficiency of the GHB resinate product and a high reaction rate on the resin. Furthermore, organic non-anionic byproducts made in reaction or present in the GBL would not be captured on the resin.

In another embodiment of the invention, one can fully load GHB on the resin, then load a lipophilic agent on the resin with higher selectivity for the resin than GHB. The agent will slow the release of GHB.

In another embodiment, one can fully load an anionic hydrophobic agent, such as stearic acid, onto the resin with lower selectivity for the resin than GHB and then subsequently load GHB less completely, thereby retaining much of the hydrophobic agent and promoting a slower release of GHB.

In still another embodiment of the invention, the hydroxide-bearing resin beads are coated with a flexible film, then loaded with GBL which, in turn, will diffuse through the film and react with the hydroxyl anions of the resin and form the GHB resinate in-situ. The coating will provide further controlled release characteristics. Examples of such coatings include films comprising polyvinyl acetate (PVAcetate), Eudragit RS, ethylcellulose, cellulose acetate or an enteric coating such as acrylic acid-based Eudragit L100, FS100 or L55, cellulose acetate phthalate, and shellac. It is understood that these films can be modified with pore formers to adjust permeability or degree of enteric protection. The coating may also be combined with suitable plasticizer and anti-tack agents to facilitate coating. Finely ground resin beads may also be encapsulated within polysaccharide gel structures that confer enteric protection, through ionotropic gelation as with calcium alginate encapsulation.

Other embodiments include reducing the amount of water in the formulation. Oral administration may be achieved while reducing the amount of water by using agents that increase flow, such as slippants to reduce viscosity. Example slippants include polyethylene oxide (PEG) (and its equivalents) which is available in various grades of varying molecular weight and molecular weight distribution.

DETAILED DESCRIPTION OF THE INVENTION

One embodiment of the invention is a GHB formulation comprising polymeric beads and pharmaceuticals acceptable excipients. The formulation can be in the form of a solid or a liquid. Additional agents, such as surfactants, may be added to control the release of GHB from within the polymeric bead, such as sodium lauryl sulfate or stearic acid. The beads can be coated with a flexible film. Background information on GHB and its related compounds, use and methods for manufacture are listed below. Also, background information on ion exchange resins, their manufacture and uses can be found in the references listed below. The new formulations of the present invention described herein provide favourable sustained release profiles for GHB.

The following U.S. patents and applications relate to GHB and are hereby incorporated by reference in their entireties for all purposes: U.S. Pat. Nos. 6,472,431, 8,263,650, 8,324,275; 8,859,619; 7,895,059; 7,797,171; 7,668,

730; 7,765,106; 7,765,107; 8,461,197; 8,591,922; 8,731,963; 8,759,394; 8,771,735; 8,772,306; 8,778,301; 8,778,398; 8,901,173; and 2012/0076865. The following patents are also incorporated by reference: U.S. Pat. Nos. 5,380,937; 4,393,236 German Patent DD 237,309 A1; and British Pat. No. 922,029.

Information on ion exchange resins, their manufacture and uses can be found in the following references which are hereby incorporated by reference in their entireties for all purposes. Mahore J. G, Wadher K. J, Umekar M. J, Bhoyar P. K., Ion Exchange Resins: Pharmaceutical Applications And Recent Advancement, International Journal of Pharmaceutical Sciences Review and Research, Volume 1, Issue 2, March—April 2010; Article 002; Munot, Neha M., et al. "Ion exchange resins in pharmaceuticals: A review." Journal of Pharmacy Research 3.12 (2010). Singh, Inderbir, et al. "Ion exchange resins: drug delivery and therapeutic applications." FABAD J. Pharm. Sci 32 (2007): 91-100; Srikanth, M. V., et al. "Ion-exchange resins as controlled drug delivery carriers." Journal of Scientific Research 2.3 (2010): 597; Singh, Inderbir, et al. "Ion exchange resins: drug delivery and therapeutic applications." FABAD J. Pharm. Sci 32 (2007): 91-100; Ohta et al., Development of a simple method for the preparation of a silica gel based controlled delivery system with a high drug content, European Journal of Pharmaceutical Sciences 26 (2005) 87-96; Akifuddin et al., Preparation, Characterization and In-vitro Evaluation of Microcapsules for Controlled Release of Diltiazem Hydrochloride by Ionotropic Gelation Technique, Journal of Applied Pharmaceutical Science Vol. 3 (04), pp. 035-042, April, 2013; Patil et al., A Review On Ionotropic Gelation Method: Novel Approach For Controlled Gastroretentive Gelispheres; International Journal of Pharmacy and Pharmaceutical Sciences, Vol 4, Suppl 4, 2012; Cabellero, et al., Characterization of alginate beads loaded with ibuprofen lysine salt and optimization of the preparation method, International Journal of Pharmaceutics 460 (2014) 181-188; J.M.C. Puguan, X. Yu, H. Kim, Diffusion characteristics of different molecular weight solutes in Ca-Alginate gel beads, Colloids and Surfaces A: Physicochemical and Engineering Aspects (2015), http://dx.doi.org/10.1016/j.colsurfa.2015.01.027; Takka and Gurel, Evaluation of Chitosan/Alginate Beads Using Experimental Design: Formulation and In Vitro Characterization, AAPS PharmSciTech, Vol. 11, No. 1, March 2010; Anand, et al., Ion-exchange resins: carrying drug delivery forward, DDT Vol. 6, No. 17 Sep. 2001. See also the Technical Information sheet for Dowex Ion Exchange Resins; the Product Data Sheet for Amberlite IRN78 Resin, both from Dow Chemicals. Also the Technical Sheet for Duolite AP143/1083 Pharmaceutical Grade Anion Exchange Resin (Cholestyramine Resin USP) from Rohm and Haas. The following U.S. Patents and applications are also incorporated by reference in their entireties for all purposes U.S. Pat. Nos. 4,221,778; 4,510,128; 6,322,819; 8,193,211, 8,202,537; 8,771,735; 8,778,398, 8,062,667, and 8,337,890; U.S. Patent Publication Nos. 2003/0180249; 2008/0003267; 2008/0118571; 2012/0076865; 2012/0148672; 2013/0273159; 2014/0004202; 2014/0093578; and 2014/0127306.

As used herein, the term gamma-hydroxybutyrate (GHB) or "oxybate" refers to the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid. The manufacture, use, known dosage forms and dosing can be shown in the above patents. An effective dosage range of Xyrem is 6 g to 9 g, given at night in divided doses approximately 2-4 hours apart. GHB is typically given twice nightly due to a short in vivo half-life. It is subject to a controlled drug distribution system. See U.S. Pat. Nos. 6,472,431, 8,263,650, 8,324,275; 8,859,619; 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 8,591,922; and 8,772,306 which are incorporated above.

One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours. As described above, a single dose is eliminated within a shorter period of time. One object of the invention is to maintain the blood level of GHB from about 10 mg/L to about 20 mg/L for up to 8, 7, 6, or 5 hours. Additionally, it is an object of the invention to ensure that the sleep inducing effects of GHB do not remain for longer than the above periods as it would compromise a patient's ability to perform normal day to day activities, such as work or driving a car. One embodiment of the invention is a controlled release formulation of GHB designed to maintain a level of GHB in the blood that satisfies the above criteria. In addition to the controlled or extended release properties of one embodiment, there can be an immediate release GHB formulation that is present in or accompanies the controlled release formulation. A sufficient amount of GHB must be present in the blood to initiate the sleep function of GHB and then the controlled release component may engage to maintain the blood concentration above the threshold for a complete sleep of sufficient duration. It has been discovered that administration of food may extend the effects of GHB in some circumstances and care should be taken to consider this effect during administration. See U.S. Pat. Nos. 8,859,619; 8,778,398 and 8,591,922 as well as U.S. Pat. Publication 2012/0076865 among others.

The buffering capacity of GHB may affect gastric pH and compromise performance of enteric-coated dosage forms. Avoidance of the potential impact on gastric pH is another useful feature of the GHB resinate, since it has no effect on gastric pH.

In one embodiment, the present invention is directed to formulations of drugs that are carboxylic acids, as described herein, and are suited to the controlled release of high dose drugs that are highly water soluble. In addition, in certain embodiments, the formulations described herein provide controlled release of drugs that are highly hygroscopic, even where such drugs must be administered at relatively high doses. In particular embodiments, the controlled release formulations are provided as a unit dose or liquid dosage form.

The formulations and dosage forms of the present invention can also include an immediate release component. The immediate release component can form part of a solid controlled release unit dosage form or liquid dosage form (e.g., combined with a controlled release GHB resinate component) or may be a separate immediate release composition. Therefore, an immediate release component may be provided, for example, as a dry powder formulation, an immediate release tablet, an encapsulated formulation, or a liquid solution or suspension. However, the immediate release component may also be formulated as part of a single dosage form that integrates both the above components. The immediate release component can furthermore be an oxybate salt such as sodium, potassium, calcium, or magnesium, the immediate release component can also comprise the GHB resinate particles without modification to retard release, or a combination of these GHB forms.

In specific embodiments, controlled release and immediate release formulations can be dosed together to a subject to provide quick onset of action, followed by maintenance of therapeutic levels of the drug substance over a sustained period of time. However, because the controlled release

component and immediate release component described herein need not be present in a single dosage form, as it is used herein, the phrase "dosed together" refers to substantially simultaneous dosing of the controlled release and immediate release components, but not necessarily administration in the same dosage form. Dosing the controlled release and immediate release components together offers increased convenience, allowing patients to quickly achieve and maintain therapeutic levels of a drug over a sustained period of time, while reducing the frequency with which the drug must be dosed. Furthermore, dosing the controlled release and immediate release components together may avoid the disadvantages of dosing regimens and formulations that result in highly pulsatile plasma concentrations.

Gamma butyrolactone (GBL) is a prodrug for GHB. It can be produced by the dehydrogenation of 1, 4 butanediol. GBL can be hydrolyzed under basic conditions (the use of a metal ion hydroxide) to produce GHB. See Arena, C, et al., "Absorption of Sodium γ-Hydroxybutyrate and its Prodrug γ-butyrolactone: relationship between n vitro transport and in vivo absorption", Journal of Pharmaceutical Sciences, 69(3), (March 1980), 356-358; and Lettieri, J, et al., "Improved Pharmacological Activity via Pro-Drug Modification: Comparative Pharmacokinetics of Sodium Y-Hydroxybutyrate and Y-Butyrolactone", Research Communications in Chemical Pathology and Pharmacology, 22(1), (1978), 107-118.

The required dose of GHB, on a molar basis, is unusually high and quite different from most pharmaceutical agents normally considered for drug-resin complexes. A 9 g dose of sodium oxybate is 71 mMol of oxybate, a carboxylic acid. This stands in contrast to a typical moderately potent active pharmaceutical ingredient (API) having a molecular weight of about 400 daltons and a dose of 400 mg, which results in a molar dose of about 1 mMol. Thus, sodium oxybate dosing is about 70-fold higher (on a molar basis) than a more typical drug.

Much of the dose is required in immediate release form for initial therapeutic benefit. However, due to the buffering effect of oxybate (pKa of 4.5), the immediate-release portion of the dose would cause the gastric pH to increase to about 6. This complicates formulation design, as rate-controlling polymers often have pH-dependent dependent solubility. In particular, if delayed release via enteric coating is desired, then upon release of the immediate release portion of the dose, the concomitant rise in gastric pH could result in at least partial dissolution of the enteric coating, thereby compromising the delayed release function of the enteric coating.

The solubility of sodium oxybate is unusually high. For example, a Xyrem solution is provided as 500 mg/mL concentration in water, or 42 wt %, and its solubility limit is considerably higher. Furthermore, due to the small size and ionic nature of GHB at physiological pH, the drug is unusually mobile in solution. Those skilled in the art will appreciate that these factors complicate and, in many cases, limit conventional approaches for modified release, such as core/shell or matrix formulations, as the high solubility and mobility of GHB would tend to significantly reduce the number of viable approaches using such conventional solubility and diffusivity control technologies.

Furthermore, while extended release oxybate dosage forms are known, such extended release dosage forms are provided as solids, e.g. as tablets. Because the required dose of oxybate is high, such tablets can be quite large, and/or require the administration of multiple tablets. This can be problematic because some patient populations have difficulty swallowing solid dosage forms, or the need to swallow multiple tablets may reduce patient compliance. In addition, the sustained release matrix or coating compositions used to provide extended release are complex and expensive to produce. Accordingly, it would be desirable to provide oxybate (or analogous drugs which require administration in high doses) in an extended release, oral liquid dosage form (including suspensions of oxybate-containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user), using simply, readily controlled processing methods.

A drug-resin complex may address some of these limitations, as the drug is essentially insoluble as long as it remains bound to the resin. Instead, the drug release is regulated by exchange with other anions present in the gut, the most prevalent being chloride. Thus, the nature of the formulation challenge is to limit the diffusion of chloride anion into the dosage form rather than to limit the egress of the soluble drug, oxybate.

Drug-resin complexes including modified release drug-resin complexes are known. However, such complexes would typically be considered unsuitable for very high dose, low molecular weight drugs such as oxybate, because the molar amount of drug required is quite high, which would therefore necessitate correspondingly large amounts of ion exchange resin, particularly if the efficiency of binding is significantly less than 100%. Accordingly, for drugs such as oxybate that are dosed at much higher molar levels, e.g., approximately 100-fold higher compared to typical drug dosing, drug-resin complexes would not be considered acceptable.

In one embodiment, a particularly convenient means of administering drug resonates is as a suspension of individual drug resinate beads. The beads may be a plurality of individual resin beads, each loaded with drug and optionally coated with a rate-controlling polymer and additives to influence its properties (such as permeability, flexibility, etc.). Coating formulations exist to address processing challenges, such as the swelling of beads and retention of film integrity. One such example is methylphenidate resinate beads as shown in U.S. Pat. No. 8,202,537.

In one embodiment, the present invention provides a GHB formulation which delivers a controlled release profile, for example a controlled release profile suitable for once-a-day dosing as described herein. Due to the prolongation of the drug release, compositions of the present invention are useful because the once-a-day dose provides a more consistent supply (release) of GHB to patients who otherwise may have to take multiple doses a day. In one embodiment, the invention provides a multi-particulate composition, for example a suspension (e.g., homogeneous suspension), or solid compositions such as a tablet, capsule, powder, wafer, or strip system comprised of a plurality of such particles and optionally other excipients.

As used herein, the term "controlled release" refers to compositions, for example GHB resinate compositions as described herein, which are characterized by having at least one of the active components having a release over a period of at least about 2 to about 8 hours, or about 4 to 6 hours, including about 2, about 2.5, about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, about 7, about 7.5, or about 8 hours, inclusive of all ranges therebetween. The release profile may be assessed using in vitro dissolution assays known to those of skill in the art, e.g., USP apparatus 2 (paddle) or, more preferably, apparatus 4 (flow-through cell). Particularly when the molar dose of

oxybate is large and approaches the amount of anion in the dissolution media, a flow-through apparatus is desired so that the media composition and flow rate can better approximate the physiologic state. The release profile can be assessed for example (e.g., for bioavailability determinations), in pharmacokinetic studies using plasma concentrations to assess maximum concentration (C_{max}) and area under the curve (AUC). Such assays are well known to those of skill in the art.

In one embodiment, the present invention provides a drug-ion exchange resin composition for further use in a formulation with conventional pharmaceutically acceptable components to provide ingestible compositions. The finished dose compositions may take the form of liquid preparations, such as suspensions, or solid preparations such as tablets, capsules, liquigels, powders, wafers, strips, etc.

Ion-exchange matrices suitable for use in these preparations are water-insoluble and comprise in most embodiments a pharmacologically inert organic and/or inorganic matrix containing functional groups that are ionic or capable of being ionized under the appropriate conditions of pH. In one embodiment, the ion-exchange matrix is anionic. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene, etc.), or partially synthetic (e.g. modified cellulose and dextrans). The inorganic matrix, in various embodiments, can comprise silica gel modified by the addition of ionic groups, or other similar inorganic materials functionalized with ionic groups. Covalently bound ionic groups may be strongly acidic (e.g., sulfonic acid, phosphoric acid), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., primary amine), weakly basic (e.g. quaternary ammonium), or a combination of acidic and basic groups. In general, the types of ion exchangers suitable for use in ion-exchange chromatography and for such applications as deionization of water are examples of materials suitable for use in the controlled release of drug preparations. Such ion-exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp: 312-343) and "Techniques and Applications of Ion-Exchange Chromatography" (pp: 344-361) in Chromatography. (E. Heftmann, editor), van Nostrand Reinhold Company, New York (1975). A high exchange capacity is desired to limit quantities of resin needed, and that typical values are about 4 mEQ/g

In one embodiment, the size of the ion-exchange particles is from about 5 microns to about 1,000 microns. In most embodiments the particle size is within the range of about 50 microns to about 750 microns (including about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 550, about 600, about 650, about 700, or about 740 microns, inclusive of all values and ranges therebetween) for liquid dosage forms, although particles up to about 1,000 micron (including the values and ranges herein, and in addition about 800, about 850, about 900, about 950, or about 1000 microns, inclusive of all values and ranges described herein) can be used for solid dosage forms, e.g., tablets and capsules. Particle sizes substantially below the lower limit are generally difficult to handle in all steps of the processing. Both uncoated and coated drug-ion exchange resin particles may be designed within this size range.

Both regularly and irregularly shaped particles may be used as resins. Regularly shaped particles are those particles that substantially conform to geometric shapes such as spherical, elliptical, cylindrical and the like, (e.g., three dimensional shapes readily described by a three dimensional space group) which are exemplified by (but not limited to) any of the ion exchange resins disclosed herein, for example Dow XYS-40010.00 and Dow XYS-40013.00 (The Dow Chemical Company). Irregularly shaped particles are all particles not considered to be regularly geometrically shaped (for example not readily described by a three dimensional space group), such as particles with amorphous shapes and particles with increased surface areas due to surface channels or distortions. Irregularly shaped ion-exchange resins of this type are exemplified by (but not limited to) any of the ion exchange resins disclosed herein, for example Amberlite IRP-69 (Rohm and Haas). Two of the resins of some of the embodiments of this invention are Amberlite IRP-69 and Dow XYS-40010.00. Both are sulfonated polymers composed of polystyrene cross-linked with about 8% of divinylbenzene, with an ion-exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H^+-form). Their essential difference is in physical form. Amberlite IRP-69 consists of irregularly shaped particles with a size range of about 5 microns to about 149 microns produced by milling the parent large size spheres of Amberlite IRP-120. The Dow XYS-40010.00 product consists of spherical particles with a size range of 45 microns to 150 microns.

In one embodiment, suitable ion-exchange resins include anion exchange resins, such as have been described in the art and are commercially available. These resins are particularly well suited for use with acidic drugs including GHB, as well as prodrugs such as GBL, salts, isomers, polymorphs, and solvates thereof, as well as other acidic drugs identified herein and/or known in the art such as salicylates, nicotinic acid, mefanimic acid, methotrexate, furosemide, phenolic drugs such as paracetamol, morphine, and levothyroxine, warfarin, phenylbutazone, indomethacin, barbiturates, phenytoin, sulphonamides, etc.

Any anion exchange suitable for pharmaceutical use can be employed in the compositions of the present invention, particularly strong anion exchange resins. An example of a suitable anion exchange resin is a cholestyramine resin, a strong base type 1 anion exchange resin powder with a polystyrene matrix and quaternary ammonium functional groups. The exchangeable anion is generally chloride which can be exchanged for, or replaced by, virtually any anionic species. Other examples include Type II resins, which contain dialkyl 2-hydroxyethyl ammonium chloride or hydroxide groups. Such Type I and Type II resins are available under the DOWEX® and Amberlite® trade names. A commercially available Cholestyramine resin is PUROLITE™ A430MR resin. As described by its manufacturer, this resin has an average particle size range of less than 150 microns, a pH in the range of 4-6, and an exchange capacity of 1.8-2.2 eq/dry gm. Another pharmaceutical grade cholestyramine resin is available as DUOLITE™ AP143/1094 (Rohm and Haas/Dow), described by the manufacturer as having a particle size in the range of 95%, less than 100 microns and 40%, less than 50 microns. The commercial literature from the suppliers of these and other resin is incorporated herein by reference (PUROLITE A-430 MR; DOW Cholestryramine USP, Form No. 177-01877-204, Dow Chemical Company; DUOLITE AP143/1083, Rohm and Haas Company, IE-566EDS—February 06). Other suitable anion exchange resins include POROS® XQ anion exchange resins available from ThermoFisher Scientific. Both regularly and irregularly shaped particles may be used as resins. Regularly shaped particles are those particles that substantially conform to geometric shapes such as spherical, elliptical, cylindrical and the like, (e.g., three dimensional shapes readily described by a three dimensional space group) Irregularly shaped particles are all particles not

considered to be regularly geometrically shaped (for example not readily described by a three dimensional space group), such as particles with amorphous shapes and particles with increased surface areas due to surface channels or distortions. The regular and irregularly shaped particles can comprise any of the anion exchange resins disclosed herein.

For the oxybate resinate compositions of the present invention, the amount of oxybate present in the resinate should be high to minimize the amount of resin required. Furthermore, in most embodiments, the amount of GHB resinate administered, expressed as GHB mEq (i.e., mmoles) is about 20 to about 120 mEq, including about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, or about 120 mEq, inclusive of all values and ranges therebetween.

The selected ion-exchange resins may be further treated by the manufacturer or the user to maximize the safety for pharmaceutical use or for improved performance of the compositions. Impurities present in the ion-exchange resins may be removed or neutralized by the use of common chelating agents, anti-oxidants, preservatives such as disodium edetate, sodium bisulfate, and so on by incorporating them at any stage of preparation either before complexation or during complexation or thereafter. These impurities along with their chelating agent to which they have bound may be removed before further treatment of the ion exchange resin with a compound to slow drug release and coating with a diffusion barrier.

Various analogous binding reactions can be carried out for binding an acidic drug to an anion exchange resin. These are (a) resin (Cl^- form) plus drug (salt form); (b) resin (Cl^- form) plus drug (as free acid); (c) resin (OH^- form) plus drug (salt form); (d) resin (OH^- form) plus drug (as free acid); (e) resin (OH^- form) plus prodrug (γ-butyrolactone). All of these reactions except (d) and (e) have ionic by-products and the anions generated when the reactions occur compete with the anionic drug for binding sites on the resin with the result that reduced levels of drug are bound at equilibrium. For acidic drugs, stoichiometric binding of drug to resin is accomplished only through reactions (d) and (e). The binding may be performed, for example as a batch or column process, as is known in the art.

Typically the drug-ion exchange resin complex thus formed is collected by filtration and washed with appropriate solvents to remove any unbound drug or by-products. The complexes can be air-dried in trays, in a fluid bed dryer, or other suitable dryer, at room temperature or at elevated temperatures which would not degrade the complex.

In one embodiment, the complexes of the present invention can be prepared by batch equilibration, in which a solution of the drug is contacted with finely divided ion-exchange resin powders. While ion exchange resins are typically provided in very fine particle sizes, which render conventional columnar ion-exchange processes inefficient, such methods can be used for ion exchange resins of suitable particle size. The total ion-exchange capacity represents the maximum achievable capacity for exchanging cations or anions measured under ideal laboratory conditions. The actual capacity which will be realized when loading a drug onto ion exchange resin will be influenced by such factors as the inherent selectivity of the ion exchange resin for the drug, the drug's concentration in the loading solution and the concentration of competing ions also present in the loading solution. The rate of loading will be affected by the activity of the drug and its molecular dimensions as well as the extent to which the polymer phase is swollen during loading.

In one embodiment, a batch or equilibrium process is used to load a drug onto an ion-exchange resin. It is usually desirable to load as much as possible of the drug, such as GHB or GBL, onto the ion exchange resin, as typical GHB doses required for treating excessive daytime sleepiness and cataplexy in patients with narcolepsy are quite high. Low loadings of GHB in the resinate would require quite large amounts of resin, resulting in unit dosages which would be too large to be conveniently administered and resin quantities that may give rise to more adverse effects such as gastrointestinal disturbance. Complete transfer of the drug from the loading solution into the ion-exchange resin is not likely in a single equilibrium stage. Accordingly, more than one equilibration may be required in order to achieve the desired loading onto the ion exchange resin. The use of two or more loading stages, separating the resin from the drug-containing liquid phase between stages, is a means of achieving maximum loading of the drug onto the ion exchange resin, although some loss of drug from the liquid phase of the final loading stage may occur.

The efficiency of loading the drug (e.g. GHB) onto the ion exchange resin can be influenced by the counter ion used in the ion exchange resin. Commercially supplied anionic resins for pharmaceutical use are almost exclusively in the chloride form. However, chloride ions have a much higher affinity for the exchange site in the resin relative to GHB. The affinity can be estimated based on the pK_a of GHB (4.44) relative to other short-chain fatty acids for which affinities are known. On that basis, GHB has approximately 18% affinity relative to chloride on the anion exchange resin. Bicarbonate, on the other hand, has an affinity of about 27% affinity relative to chloride. Therefore, when a bicarbonate-exchanged resin is contacted with GHB, a much higher efficiency of GHB incorporation may be achieved, because the affinity of GHB relative to bicarbonate is about 67% vs. about 18% relative to chloride. Other "intermediate" exchange anions can also be used, especially those with low affinity relative to chloride and much lower cost relative to oxybate. Thus in some embodiments, substantially all of the chloride counter ion of the e.g. commercially available pharmaceutical grade anion exchange resin is replaced with the intermediate anion (e.g. bicarbonate), in one or more batch equilibration steps as required. After rinsing with an appropriate solvent, the ion exchange resin exchanged with the lower affinity anion (relative to chloride) can then be then exchanged with oxybate.

Substantially complete incorporation (i.e., expressed as the percentage of theoretically available ion exchange sites) of oxybate in the anion exchange resin is desirable to minimize the amount of anion exchange resin required to provide a specified dose of drug (e.g. oxybate). In practice, 100% incorporation of the drug can be difficult and/or expensive to achieve, so somewhat less than substantially complete levels of incorporation of drug are also suitable. Typically, levels of incorporation of more than about 75% are acceptable, including about 75%, about 80%, about 85%, about 90%, about 92%, about 94%, about 96%, about 98%, about 99%, or about 100%, inclusive of all values and ranges therebetween.

When a multi-step batch equilibration is needed or desirable, the resinate slurry formed during equilibration can be decanted to remove the solution of oxybate. The decant can be collected for potential recovery of oxybate or waste disposal. The resinate is then rinsed with solvent, such as de-ionized water, and then charged to the batch equilibration

tank where it is contacted with fresh or recovered oxybate to increase the level of incorporation of oxybate. Multiple equilibration steps can be used with fresh or recycled oxybate solution until the desired level of incorporation, as described herein, is achieved.

Recovery of oxybate from a chloride-exchange process can be very challenging due to oxybate's high water solubility and relatively small size. If aqueous processing is used, all chloride salts are soluble. However, when an intermediate anion (e.g. bicarbonate) is used, the solubility can be manipulated with selection of the cationic form of oxybate. If full and complete exchange of oxybate is desired in one step, then the salt form of oxybate is selected such that the salt form of the exchanged anion is insoluble. For example, calcium salts of many exchangeable anions tend to have very low solubilities. Oxybate can be introduced as calcium oxybate, which is highly water-soluble and suitable for an aqueous exchange process. Precipitation drives the exchange process to near-completion, resulting in very high oxybate yield and incorporation. For example, bicarbonate would precipitate as calcium carbonate if the relatively insoluble calcium hydroxide is added in stoichiometric amount at the commencement of batch equilibration, as shown below. Other example intermediate examples include phosphate (precipitating as calcium phosphate), sulfate (precipitating as calcium sulfate), and hydroxide (precipitating as calcium hydroxide).

$$Ca^{++}(GHB^{-})_2+2R—HCO_3 \rightarrow Ca^{++}+2HCO_3^{-}+2R—GHB;R=resin$$

$$Ca^{++}+2HCO_3^{-}+Ca(OH)_2 \rightarrow CaCO_3(s)+H_2O$$

Use of precipitation as a means to drive batch equilibration can result in some difficulties in recovering the resin, as the resinate and precipitate can both be small particles. In some embodiments, the exchange process is carried out under conditions such that all species remain soluble, and therefore the resinate and solution are easily separated. Next, the oxybate is recovered from the solution in a separate vessel by performing a displacement precipitation by addition of another salt or base. For instance, in the above example, the calcium hydroxide can be added in a separate step, thereby avoiding a difficult separation problem. Although this process may provide a somewhat less efficient equilibration per batch cycle, recovery of the un-exchanged oxybate can be nearly 100%, and multiple batch equilibrations can be performed economically. The technique can be more generally applied if sodium oxybate is used in the exchange process, because most sodium salts of the exchanged anion would remain soluble. In the recovery step, a calcium salt or base is added in near-stoichiometric amount to precipitate the exchanged oxybate and enable full recovery of the sodium oxybate. In one embodiment, calcium hydroxide is added to facilitate recovery. Because it has low solubility, calcium hydroxide can be used in excess without appreciably contaminating the recovered sodium oxybate with calcium.

$$Na^{+}GHB^{-}+R—HCO_3 \rightarrow Na^{+}+HCO_3^{-}+R—GHB;R=resin$$

$$2Na^{+}HCO_3^{-}+Ca(OH)_2 \rightarrow CaCO_3(s)+2H_2O$$

In yet another embodiment of processes for forming the GHB resinate, the anion can be recovered by sub-stoichiometric addition of the soluble calcium oxybate to the sodium-exchanged intermediate anion in the recovery process. Most of the sodium oxybate can be recovered and recycled without causing precipitation during the batch equilibration.

In a particular embodiment, bicarbonate can be evolved as CO_2 gas and the sodium ions form sodium oxybate by adding GBL. This avoids a potentially difficult separation of precipitate during recovery. The sodium bicarbonate is first converted to sodium carbonate, and then the sodium carbonate is reacted with GBL to yield sodium oxybate and carbon dioxide as shown below.

$$NaOH+NaHCO_3 \rightarrow Na_2CO_3+H_2O$$

$$2GBL+Na_2CO_3+H_2O \rightarrow 2Na—GHB+CO_2(g)$$

In yet another embodiment, the bicarbonate form of an anion exchange resin (e.g., and type 1 strong base anion exchange resin), prepared, for example by ion exchange of the chloride form with sodium or potassium bicarbonate (or other soluble bicarbonate salts), is equilibrated with a solution of sodium or potassium oxybate. The resulting oxybate resinate can be separated from the oxybate equilibration solution by known methods (decanting, filtering, etc.). The oxybate equilibration solution can then be treated with sodium or potassium hydroxide to increase the pH, and then contacted with GBL. At the elevated pH, the GBL reacts with exchanged bicarbonate to form additional GHB (oxybate) and carbon dioxide, thereby regenerating the oxybate equilibration solution so that it can be reused, as the bicarbonate ions produced during the initial ion exchange/equilibration step is lost as carbon dioxide gas. The regenerated oxybate equilibration solution can then be re-equilibrated with the oxybate resinate formed in the initial equilibration step, so as to further increase the degree of exchange of oxybate in the resinate. The regenerated equilibration solution can be further regenerated, and further equilibrated with the oxybate resinate as many times as is needed or desired to obtain the desired degree of incorporation of oxybate in the oxybate resinate. A further advantage of this method is the minimization of oxybate waste due to the ability to regenerate and recycle the oxybate equilibration solution.

High loading capacity will be favored by high charge density in the drug. A high loading rate is favored by lower molecular weight. Higher drug concentrations in the loading solution, with a minimum of competing ions, will also favor higher adsorption capacity.

Thus, in one aspect, the invention provides drug-ion exchange resin complexes comprising a drug loaded in an ion exchange resin as described herein. The drugs and ion exchange resins may be readily selected from amongst those drugs and resins described herein. In most embodiments, GHB and GBL are suitable drugs. The invention further provides drug-ion exchange resin matrixes defined as follows.

The drug-ion exchange resin complexes of the present invention can readily be formulated with pharmaceutically acceptable excipients according to methods well known to those of skill in the art, for example as described in Remington, The Science and Practice of Pharmacy, 22 Edition Philadelphia College of Pharmacy 2013 Pharmaceutical Press, herein incorporated by reference in its entirety for all purposes. In one embodiment, these formulations contain a substantially coated drug-ion exchange resin complex of the invention, optionally with a compound that will slow the release of the drug. In another embodiment, such formulations may also contain a selected amount of uncoated drug-ion exchange resin complex, optionally with a compound to slow the release as described herein. In certain

formulations, mixtures of coated drug-ion exchange resin complexes and uncoated drug-ion exchange resin complexes are present. These formulations may contain any suitable ratio of coated to uncoated product.

In one embodiment, the controlled release dosage form includes drug loaded onto beads (e.g., ion-exchange beads) in combination with one or more optional excipients, such as binders, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, lubricants, glidants, or other suitable excipients. In one embodiment of the compositions of the present invention that can be fashioned into a tablet or other solid form, beads containing GHB or GBL can include one or more binders that are known for use in tablet formulations. In one such embodiment, the solid form may include at least one binder selected from hydroxypropyl cellulose (HPC), ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate. In specific embodiments, the solid form included in a controlled release dosage form as disclosed herein may comprise binder levels ranging from approximately 1% to 10% by weight. For example, the CR core may include a binder in an amount selected from about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, and 10% by weight, including all ranges therebetween. In certain such embodiments, the amount of binder included in the CR core may range from about 1 to 2%, 1 to 3%, 1 to 4%, 1 to 5%, 1 to 6%, 1 to 7%, 1 to 8%, 1 to 9% and 1 to 10% by weight.

One formulation of the present invention may include one or more lubricants to improve desired processing characteristics. One embodiment of the present invention may include one or more lubricants selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added in a range of about 0.5% to 5% by weight. Particular embodiments may comprise a lubricant in a range of about 0.5% to 2% by weight, about 1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight, inclusive of all ranges therebetween. Still lower lubricant levels may be achieved with use of a "puffer" system during tabletting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation. When "puffer" systems are used for tabletting, the compositions of the present invention can, but need not be, substantially free of lubricant (e.g., include only traces of lubricant deposited by contact with the lubricant coated tablet press).

In certain embodiments, where the compositions of the present invention are provided as liquid compositions, such as suspensions, the compositions of the present invention can further comprise colorants, flavoring agents (natural and artificial), stabilizing agents (EDTA salts, parabens, benzoates), thickeners (tragacanth, xanthan gum, bentonite, starch, acacia, cellulosics), humectants, sweeteners (sucralose, acesulfame K, saccharides, sorbitol, xylitol, mannitol, maltose), etc.

In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof. In certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alphahydroxy carboxylic acid. In certain other embodiments, the acid is selected from the group including, but not limited to, acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like. In a preferred embodiment, the acid is malic or hydrochloric acid. In certain other embodiments, the pH adjusting agent may be a base selected from the group including, but not limited to, acetanilide, ammonia, apomorphine, atropine, benzocaine, caffeine, calcium hydroxide, cocaine, codeine, ephedrine, morphine, papaverine, physostigmine, pilocarpine, potassium bicarbonate, potassium hydroxide, procaine, quinine, reserpine, sodium bicarbonate, sodium dihydrogen phosphate, sodium citrate, sodium taitrate, sodium carbonate, sodium hydroxide, theobromine, thiourea or urea. In certain other embodiments, the pH adjusting agent may be a mixture of more than one acid and/or more than one base. In other preferred embodiments, a weak acid and its conjugate base are used to form a buffering agent to help stabilize the composition's pH.

Additionally, any excipient, salt, acid, pH-mediating, adjusting or buffering compound or agent, flavoring, solution, solvent, dispersion, glycerol, glycol, oil, antibacterial and antifungal agents, antibiotics and antihistamines, binders, disintegrating agents, lubricants, sweetening agents, or any other additive or ingredient from those enumerated above or in the examples, or in any pharmaceutically acceptable composition or carrier described herein, or as would be known by one of skill in the art, is contemplated for use in aqueous mediums or solid forms of the GHB compositions of the invention. One or more of these compositions may be packaged with GHB or packaged separately from GHB prior to consumption. If packaged separately, useful compositions of GHB may be obtained by mixing GHB with the other components with an aqueous medium prior to consumption.

In certain embodiments, the pharmaceutical composition may also contain an antioxidant. An "antioxidant" is understood herein to mean certain embodiments which are substances that inhibits oxidation. Such antioxidants include, but are not limited to, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite, anoxomer and maleic acid BP.

In some embodiments of the formulations of the present invention, the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof.

The drug-ion exchange resin composition thus prepared may be stored for future use or promptly formulated with conventional pharmaceutically acceptable carriers to prepare finished ingestible compositions for delivery orally, or via other means. In one embodiment, a tablet of the invention is formulated as an orally disintegrating tablet. Such

orally dissolving tablets may disintegrate in the mouth in less than about 60 seconds. See U.S. Patent Publication. 2012/0076865.

In one embodiment, the oral liquid compositions of the present invention may also comprise one or more surfactants in amounts of up to about 5.0% w/v or from about 0.02 to about 3.0% w/v of the total formulation. The surfactants useful in the preparation of the finished compositions of the present invention are generally organic materials which aid in the stabilization and dispersion of the ingredients in aqueous systems for a suitable homogenous composition. In particular embodiments, suitable surfactants are non-ionic surfactants such as poloxamers, polyoxyethylene ethers (BRIJ), alkoxylated fatty acids (MYRJ), polysorbates (TWEENs), macrogol mixtures (Gelucire, Labrasol), and sorbitan esters (SPANs). These are produced in a wide variety of structures and molecular weights.

When present, the surfactant component may comprise from about 0.01 to about 2.0% w/v of the total composition (for example 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2.0% w/v, inclusive of all ranges therebetween) and in particular embodiments will comprise about 0.1% w/v of the total of the composition. One or more additional emulsifiers or surfactants can also be employed in one embodiment of the invention.

The sustained-release profiles of drug can be obtained by using a mix of uncoated and semipermeable coated resonates and by selecting the degree of cross-linking and particle size of the resins without a coating process. Examples of ion exchange resins include simple resonates (i.e., uncoated drug-ion exchange resin complexes), microencapsulated or coated resonates (i.e., coated drug-ion exchange resin complexes), hollow fiber systems (i.e. hollow fibers with drug containing lumen), sigmoidal-release systems. Examples of such drugs are frusemide, cyclosporin, allopurinol and ciprofloxacin. See Mahore et al. Formulation of such drugs as resonates according to the present invention permits particle sizes that make such release characteristics (e.g., sigmoidal) feasible at reasonable coating weights.

Some embodiments of the present invention involve direct synthesis of oxybate resinate from one or more precursors. Using a hydroxide-form Type 1 strong base anion exchange resin, essentially 100% loading efficiency can be achieved with a simple aqueous reaction with GBL.

The ability to prepare an oxybate resinate, at high loading, in a one step process from GBL can be amenable to point-of-use synthesis (either in patient's hands or at clinical site), as it does not involve shipping or handling the regulated API (GHB). Such a direct synthesis can be carried out using a batch or equilibrium process as described herein, wherein a GBL loading solution is contacted with the particulate hydroxide-form strong base anion exchange resin. The GBL reacts in situ to form an ionic complex of oxybate with the ion-exchange resin, and releasing water as a by-product. It is possible to get 100% yield as well as 100% loading efficiency (i.e., oxybate ionically bound to 100% of the available binding sites) on the resin by such processes. For example, loading efficiencies higher than about 65% (e.g., 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, or about 100%, including ranges therebetween, can be achieved). Because GBL is uncharged and the reaction does not produce ionic byproducts, there are no anions to compete for reaction on the site. Such conditions can achieve 100% reaction on the resin, so the hydroxide-form resin can be used safely, whereas in other applications this may not be possible for patient safety reasons because any unexchanged hydroxide would leave the resin as sodium hydroxide, raising the pH at site of delivery and potentially causing gut wall irritation.

The one-step process is also advantageous because it simplifies purification of the GHB resinate. Because the reaction occurs on the resin and not in the bulk solution, any byproducts that would be made are rinsed off the product. These include any of the impurities in the GBL starting material, as well as unreacted GBL.

Because of the unusually large molar amount of GHB in the compositions of the present invention, relative to the molar quantity of anion present in the gut, the present inventors have found that the compositions of the present invention can provide sustained release without the use of diffusion controlling coatings on the resinate particles. The present inventors have recognized that because the volume and anion content of gastric juice in the fasted state is lower than the molar dose of GHB required for treating the conditions described herein, the rate of GHB release is strongly influenced by the rate of physiological production of anions, and therefore suitable GHB release profiles can be provided without the use of diffusion controlling coatings. For example, while the resinate beads are retained in the stomach, the release of GHB from the resinate beads provided by ion exchange with gastric ions (mainly Cl^-) can be limited by the rate of stomach acid secretion. Similarly, as the resinate beads transit the duodenum and small intestine, the remaining dose of bound GHB can exceed local anion capacity. Thus, the rate of GHB release can be limited by the rate of secretion or diffusion of anions into the gut.

The basal anion capacity of the GI tract is quite small. As summarized in McConnell (Int J Pharm 2008, 364: 213-226, Table 1), fasted state basal values of bile salts are so low that they may be ignored. The fasted state chloride balances are 4.6 mEq in the stomach and 13.1 mEq in the small intestine. Compared to an oxybate dose of about 100 mEq, there is almost an order of magnitude deficiency in resident anion capacity for exchange. Such a situation would not occur with the vast majority of drugs having doses in the <1 mMol range.

	Stomach	Small intestine
Volume, mL	45	105
Chloride, mM	102	125
Total mEq	4.6	13.1

Therefore, the present inventors have discovered that the release of the ion-exchange resin-bound oxybate can be limited by secretions of anions in the GI tract, of which chloride is dominant. In the stomach, basal acid output (as chloride) is about 3 mEq/h in the fasted state. Even in the event that fed-state behavior is induced upon dosing, the fed state maximum secretion is only about 25 mEq/h. Therefore, the stomach cannot support full exchange at rates required to impart a meaningful duration of effect.

Chloride is actively secreted in jejunum, at a rate of about 4 mEq/h/30 cm under conditions where 120 mM chloride is already present. (Davis GR, et al, Active chloride secretion in the normal human jejunum, J Clin Invest 66:1326-1333 (1980)) This translates to a basal rate of about 32 mEq/h in absence of a chloride gradient. In presence of a gradient, the present inventors have found that the contribution of passive

diffusion can be sufficient, but may still provide a meaningful impediment to full and timely release of oxybate from the resin.

In the ileum, chloride secretions are substantially less, as characterized by Turnberg. (Turnberg LA et al, Interrelationships of chloride, bicarbonate, sodium, and hydrogen transport in human ileum, J. Clin Invest, 49: 557-567 (1970)). Most chloride secretion is associated with bicarbonate exchange when levels are high. One skilled in the art would appreciate that the perfusion studies by Turnberg indicate that chloride secretion in the ileum would almost certainly be insufficient to support the required exchange with GHB-resinate. For example, even in the extreme case where bicarbonate is almost 90 mM and chloride is only 40 mM, the chloride secretion—taking into account the whole length of ileum—would be expected to be at most 23 mEq/h. In the more typical case where bicarbonate is 40 mM, chloride is actually absorbed rather than secreted—even when chloride levels are set at 40 mM. Yet ileal fluid is maintained isotonic.

To further add to the limitations of biology, the reservoir of small intestinal fluid is small and not well distributed. Only about 10% of the physical volume of the small intestine is filled with fluid. The fluid is not continuously and evenly distributed, as reported by Schiller (Schiller C, et al, Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging, Aliment Pharmacol Ther 2005; 22:971-979) but rather the majority of fluid exists in about 4 fluid pockets that access a relatively small amount of available surface area. This is not very limiting for non-resinate dosage forms, as long as drug dissolution can occur, as once the drug is dissolved, it can access most of the surface area of the small intestine for absorption. A resinate, on the other hand, requires exchange with dissolved anions in order to provide release of the drug. As exchange occurs, oxybate is released to, and chloride is depleted from, the surrounding fluid. Further exchange is limited until oxybate is absorbed and chloride is replenished in the surrounding fluid—both processes that require fluid contact with intestinal surface. Therefore, if only 10% of the intestinal surface is physically available at any given time, the rate of chloride replenishment must be 10-fold higher to reliably compensate. One skilled in the art considering these unusual aspects would conclude that, in the face of insufficient resident anion capacity in the small intestine, a resinate dosage form would not release its drug completely and, furthermore, what release occurs may not be well-regulated.

Given the above observations, permeability and amount of film may require adjustment to achieve the intended release profile.

Optionally, the release of GHB can be tailored by changing the bead size and/or degree of crosslinking of the beads to provide additional resistance to diffusion. For example, larger resinate beads have a lower surface area/volume ratio than smaller resinate beads, and therefore would release GHB more slowly than the smaller beads in the presence of a solution of the same ionic strength. Similarly, the degree of crosslinking of the beads relates to the degree of swelling of the beads, which in turn is related to the rate at which ion exchange, and this drug release can occur. Specifically, more highly crosslinked beads swell less, and thus have slower ion exchange kinetics, compared to less highly crosslinked beads, Thus, the kinetics of drug release can also be controlled by manipulating the degree of crosslinking of the beads. Effects of particle size, particularly 100 microns or greater, and crosslinking, particularly 4% or greater, that may be modest under normal circumstances may be more impactful in the absence of a rate-controlling coating and when gut anion concentrations are substantially diminished.

If no diffusion controlling coating is required, other processing schemes for making the resinate can be considered to improve manufacturing flexibility. For example, instead of using ~100 micron beads, the drug (e.g., GHB or GBL) can be loaded onto larger beads (e.g., 600 micron beads), and then ground to the desired particle size, particle size distribution, consistency, etc. to select or control the desired release characteristics. This could be carried out in an aqueous suspension, so that no isolation or drying of the resinate would be needed. Moreover, if there is no need to coat the particles (e.g., with a diffusion for coating), the irregular shape or dispersity in size distribution of ground particles, which is normally a complicating factor for coating processes, is not an issue.

In other embodiments, the compositions of the present invention can provide differential displacement of drug (e.g. oxybate) from the resinate. Core/shell release characteristics in the resinate beads can be provided by (a) loading oxybate onto an ion exchange resin such that complete loading is achieved, then (b) coating the beads with a portion of lipophilic agent (i.e. lipophilic anion) having much higher selectivity for the ion-exchange resin than GHB. The lipophilic agent will deposit in the outer shell, at the first sites it contacts, and will be relatively immobile resulting in reversible blockage of the bead pores. Suitable lipophilic agents would be, for example, sulfate salts of medium or long-chain fatty acids, such as sodium lauryl sulfate (SLS), or sulfonic esters, such as dioctyl sulfosuccinate (docusate). Other suitable agents may include alkylbenzene sulfonates, 2-naphthalene sulfonate, phenol, salicylic acid, or any other species that may bind more strongly to the resin than oxybate. In particular embodiments, the lipophilic agents are those which are bulky or present hydrophobic tails that may further hinder diffusion of chloride into the resin pore, or oxybate out of the pore after exchange. Although many effective agents may, in other contexts present toxicity concerns, because such agents are strongly bound to the resin, exposure of the agent to the patient is limited. In one embodiment, the lipophilic agent acts as a diffusion barrier both by blocking pores and by facilitating pore blockage by other hydrophobic agents, for example those added during manufacturing, or which may be present in the patient's digestive tract after administration. For example, if sufficient amounts of a surfactant such as SLS is employed, then a non-ionic hydrophobic agent may be more effectively introduced into the bead pore volume due to its compatibility with the hydrophobic "tail" of the SLS molecule. This provides retarded initial release of the drug (e.g., GHB). In other embodiments, further heat treating of the resinate beads can reduce the variability of release, or further retard release. In other embodiments the compositions of the present invention can comprise more than one population of beads, in which one or more of the bead populations is treated with a lipophilic agent, a combination of a lipophilic agent and a hydrophobic agent, or heat treated to as to provide the desired release characteristics. For example, untreated beads would provide more immediate or faster release, and treated beads would provide delayed or slower release.

If further control of release is needed, in a further embodiment the present invention provides a novel method for preparing GHB-containing resinate beads coated with a diffusion rate controlling coating. This embodiment takes advantage of the driving force supplied by reaction of GBL on the active (hydroxide-bearing) sites of hydroxide-form

ion exchange resin beads, and the relatively high diffusion characteristics of the small and uncharged GBL molecule. Hydroxide-form ion-exchange resin beads (of any size) can be coated with a flexible film, such as PVAcetate, Eudragit RS, cellulose acetate 398, a mixture of Eudragit RS/RL or Eudragit NE, ethylcellulose, or an enteric such as Eudragit L100, L55 or FS100 with suitable plasticizer. The coated ion-exchange resin beads are then suspended in de-ionized water to equilibrate. GBL is introduced to the suspended beads, which then diffuses through the rate-controlling film, and reacts progressively with the OH-bearing sites within the resin. Sufficient batch equilibration time is provided to ensure complete reaction. The excess GBL is washed off, and the resulting wet resinate beads have a sustained release coating over GHB resinate, which were formed without starting with GHB resinate. This process may be useful for point-of-use preparation, or can improve the utilization of GBL in preparing the product: no GHB or GBL is lost due to processing during coating, as no GBL is present during the coating process.

In one embodiment of the present invention, the present formulation is administered to a patient once nightly. The patient is administered between 4 g and 10 g GHB/day, or 6 g and 9 g/day. Any of the compositions described herein can be used to provide retarded or delayed release of GHB. For example, the GHB resinate beads may be presented in hydrated form as part of an aqueous suspension, or may be provided as dried beads for mixing with water immediately prior to ingestion or to be taken without water (e.g., as a powder, tablet, capsule etc.). As discussed herein, Type 1 strong base anion exchange resins swell in the presence of water, to an extent that depends on the degree of crosslinking and the nature of the anion bound to it. In the dried state, the sustained release resinate beads of the present invention can hydrate more slowly if release-retarding agents are used. As the beads hydrate, the diffusion of physiologically produced anions of the gastrointestinal tract (e.g. mainly chloride) into the beads can accelerate, thus producing a delayed or gradually increasing rate of release of oxybate.

In another embodiment, a water permeable but relatively insoluble coating is employed over the dry resinate beads such that, when the dry beads are suspended in water, water diffuses through the coating to hydrate and swell the resinate beads. The resulting expansion of the beads causes the coating to rupture, and allow release of the GHB. Suitable polymers for preparing such coatings include one or more of cellulosics such as ethyl cellulose, cellulose acetate, cellulose phthalate; polyvinyl acetate, acrylic polymers and copolymers such as those available under the Eudragit® trade name (e.g., Eudragit® NE30D, RL, and RS resins). Such coatings can be plasticized or unplasticized, and coated onto the beads using methods well-known in the art (pan coating, fluidized bed coating, etc.).

As discussed herein, the dose of GHB required for treating excessive daytime sleepiness and cataplexy in patients with narcolepsy is quite high, resulting in the administration not only of relatively large masses of GHB composition, but also water required for administration (particularly when the GHB composition is aqueous). However, since oxybate is administered at night, administering large quantities of water can cause bed-wetting. Accordingly, if administered as an aqueous suspension, the highest practical solids loading is desired. The factors which affect the solids loading (volume fraction) of the suspension include the medium used for dilution (water vs. alcohol) and its viscosity, the degree of swelling of the resinate, the sphericity and uniformity of the beads, and surface charge. See Seno and Yamabe, The Rheological Behavior of Suspensions of Ion-Exchange Resin Particles, Bulletin of the Chemical Society of Japan Vol 39, 776-778 (1966), herein incorporated by reference in its entirety for all purposes. In various embodiments, the compositions of the present invention can be administered as suspended resinate particles in a gel, suitable for ingestion by squeezing from a pouch. In other embodiments, the compositions of the present invention can be dosed in two stages: an initial loading dose followed by a chasing dose. Both the loading and chasing dose comprise suspended beads, but the chasing dose is less concentrated. In still other embodiments, the GHB resinate beads can be administered dry, e.g. by having the patient suck the dry beads through a tube or straw. In such embodiments, an added glidant, which is an excipient used in the art to facilitate powder flow by reducing interparticle friction and cohesion, can be used to facilitate administration. They are used in combination with lubricants as they have no ability to reduce die wall friction. Non-limiting examples include fumed silica, talc, and magnesium carbonate.

The oxybate resinate compositions of the present invention can include an immediate release and an extended release component of oxybate. Such compositions can include, for example, a combination of a population of uncoated resinate beads and a population of resinate beads with a diffusion rate controlling coating as described herein; a single resinate bead population that provides immediate release by ion exchange with physiological anions (e.g. chloride), followed by extended release of oxybate controlled by physiological production of e.g. chloride; combinations of populations of resinate beads having different particle sizes and/or crosslinking densities to control release; or any combination of immediate release and extended release resinate beads disclosed herein.

In one embodiment, the compositions of the present invention may be an immediate-release alternative to Xyrem®. Xyrem® has a steep dose-response curve, and inadvertently taking two doses at the same time would have an adverse effect on the patient. If sodium oxybate is instead provided in resinate form for immediate release, as described herein, the capacity of the stomach and small intestine to provide exchangeable anion would limit the consequences of an inadvertent overdose. A 4.5 g dose of Xyrem is 35.7 mEq oxybate. If the stomach has about 5 mEq chloride, then about 30 mEq of additional exchangeable anion must be provided with the resinate formulation of the present invention to ensure complete release of oxybate. This can be achieved by inclusion of exchangeable anion in the formulation, for example glycine or other amino acids, chloride, or in particular citrate. This embodiment would enable rapid release of the oxybate by providing supplementing exchangeable anions in the stomach.

In another embodiment, the supplemental anions are provided by digestion of proteins administered with or as part of the formulation. The resulting amino acids are then available for exchange with the resin and can provide a more convenient means of providing a large amount of supplemental anion.

In yet another embodiment, the supplemental anions are provided by digestion of a triglyceride administered with the formulation. When the triglyceride empties into the small intestine, lipolysis will generate anions available for exchange. In general, triglycerides of short-chain fatty acids (such as triacetin or tributyrin) can provide better oxybate release than medium- or long-chain triglycerides, because the binding affinity of the resulting anions are higher due to their pKa and size. Triglycerides with at least one short-

chain fatty acid component are also suitable, particularly pharmaceutically acceptable short-chain triglycerides such as triacetin.

If the resinate particles are film-coated, then supplemental anions can be provided as separate coated particles, such that the supplemental anion is available when needed. The supplemental anion can be selected such that it is not absorbed rapidly yet has an affinity for the resinate that is much higher than that of oxybate. It can be particularly useful to target or enhance release of the supplemental anion in the ileum where chloride secretory deficit may be most pronounced, since absorption of organic acids might be considerably less in that location. Citric acid, glycine, and mesalazine (5-aminosalicylic acid) are examples of suitable supplemental anions. A non-limiting list of other suitable anions (or conjugate acids) includes pharmaceutically acceptable salts selected from the group consisting of chlorides, acetates, lactates, bicarbonates, sulfates, citrates, tartrates, malates, maleates, malonates, glutarates, succinates, fumarates, aspartates, glutamates, and combinations thereof.

These supplemental anions can be coadministered with the oxybate compositions of the present invention, for example within about an hour (before or after) of administering the drug resinate (e.g., oxybate resinate) compositions of the present invention, or simultaneously therewith. The amount of such supplemental anions can range from about 20 to about 200 mmoles, including about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, about 120, about 125, about 130, about 135, about 140, about 145, about 150, about 155, about 160, about 165, about 170, about 175, about 180, about 185, about 190, about 195, or about 200 mmoles, inclusive of all values and ranges therebetween. The supplemental anions can themselves be capable of anion exchange directly upon contact with the drug resinate (e.g., exchanging with the oxybate of the oxybate resinate), or can be "pro-anions"—that is, form anions upon biotransformation after administration to the patient. Non-limiting examples of such "pro-anions" are those described herein, such as triglycerides or proteins. The amount of such "pro-anions" suitable for use in treating patients according to the present invention are amounts that produce between about 20 and about 200 mmoles of anions, as described hereinabove.

If sustained release is desired, then extending gastric emptying can somewhat compensate for deficiencies in the jejunum and, particularly, the ileum. Reliably extending gastric emptying in the fasted state is very challenging. Although some investigators have found that administration of resinate particles can result in mucoadhesion, the unusually high molar doses of GHB of the resinate compositions of the present invention, approximately 100 mEq, will effectively cover the entire surface of the stomach many times over. Thus, observations made with conventional resinate formulations would not apply to GHB resonates. Therefore, a more effective means of promoting gastric retention would be administration of the compositions of the present invention with food or caloric liquid.

The oxybate compositions of the present invention, for example oxybate resinate compositions, provide therapeutically effective levels of oxybate over a period of at least about 3 to about 8 hours. In some embodiments, the composition can be considered to comprise a single population of resinate beads, wherein at least a portion of the resinate beads releases the oxybate quickly upon administration (essentially upon contacting physiologically produced anions such as chloride), and a remaining portion of the resinate beads releases oxybate more slowly, either controlled by the physiological rate of production of anions such as chloride, or by modification of the release characteristics of the resinate beads themselves (e.g., by providing a diffusion controlling coating, by control of bead diameter, or crosslinking density, or other method as described herein). If the compositions of the present invention comprise two or more distinct bead populations (distinguished by their oxybate release characteristics), the rapid (or immediate) release population provides therapeutically effective levels of oxybate for up to about 3 hours (including 1 or 2 hours) after administration, and the other population(s) provide therapeutically effective levels of oxybate for about 3 to about 8 hours (including 3, 4, 5, 6, 7, or 8 hours) after administration.

Xyrem for its approved indications is effective at between 6 g and 9 g administered twice nightly in equal amounts about 4 hours apart. A sustained release equivalent may require a matching AUC as compared to 9 g Xyrem. As disclosed in US2012076865, the overall relative bioavailability of an appropriately-timed sustained release would have at most about 75% relative to Xyrem. Therefore, about 12-13 grams of sodium oxybate would be required, or about 100 mMols.

Suitable blood levels of oxybate are at least about 10 mg/L, ranging up to about 70 m/L, maintained over a period of about 5-8 hours as described herein. For example suitable blood levels of oxybate can be about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, or about 70 mg/L, inclusive of all ranges therebetween.

The following examples are included to demonstrate particular embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute particularly suitable modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

All documents cited herein, including patents, patent publications, and non-patent publications are herein incorporated by reference in their entirety for all purposes.

EXAMPLES

Example 1

A gel-type Type 1 strong base anion exchange resin, Dowex 1X2 (Dow Chemical), 100-200 mesh was loaded with GHB as follows. Calcium oxybate was loaded onto resin in a batch equilibration by combining 10 mL of 4 M calcium oxybate solution (approximately 490 mg/mL), 31.7 mL of de-ionized water, and 20.27 g of Dowex 1X2 wet resin as chloride form with 2% crosslinking. After mixing for 2 hours, the resin was filtered under mild vacuum using a Buchner funnel. It was then washed with 700 mL of de-ionized water in approximately 100-150 mL aliquots to remove any free oxybate. The wet beads were then dried in a 60° C. oven for 3.5 hours, and finally sized through a 36-mesh screen. The resinate beads were assayed by suspending 1.5 g of resinate in 12.5 g of 1 M calcium chloride and allowing them to equilibrate overnight at room tem-

perature. The solution was analyzed by HPLC, and the measured oxybate released from the beads was 1.09 mEq per gram of dry resinate. The calculated loading efficiency was 1.14 mEq/gram dry resin, or 33% of the theoretical exchange capacity of the resin.

Example 2

GHB resinate beads were prepared by contacting GBL with another Type 1 strong base anion exchange resin (Amberlite IRN78, Dow Chemical) having a median particle size of about 0.63 mm, as the hydroxide form with 8% crosslinking. Batch B1 was prepared with a 2:1 molar ratio of GBL to hydroxide-bearing sites by suspending 26.78 g of wet resin in 41.2 g of de-ionized water. While stirring, 8.28 g of GBL was added, and the reaction was monitored by HPLC analysis of unreacted GBL. The reaction was largely complete after 30 minutes. After 90 minutes, the resin was filtered under mild vacuum, rinsed with de-ionized water to remove unreacted GBL, and then placed in a 60° C. oven overnight to dry.

Batch B2 was prepared by reacting GBL in only 16% molar excess over hydroxide-bearing sites on the same resin. 2.6 g of GBL was added to 20 g of wet resin (as supplied) while stirring by hand with a spatula. About 5.3 g of additional water was added to facilitate blending. After about 1 hour, the mass was placed in the 60° C. oven overnight to complete the reaction, if necessary. The beads were then rinsed with de-ionized water (70 mL), filtered under mild vacuum, and transferred to the 60° C. oven for drying over 3 days. The two batches were analyzed for oxybate content by first suspending 1.0 g of resinate in 20 mL of 2 M NaCl for 2 hours with stirring. 10 mL of the resulting solution was then titrated with 1 N HCl and the results were compared with a blank of 10 mL of 2 N NaCl. The initial pH values of B1 and B2 were 7.0 and 8.3, respectively, thus indicating that very little, if any, unreacted hydroxide was present in the resinate product. The oxybate titration indicated that GHB loadings of 4.2 and 4.3 mEq/g dry resin for B1 and B2, respectively. The result further indicates that complete reaction occurred, as the theoretical capacity of the resin is approximately 4 mEq/g.

Example 3

A larger batch of GHB resinate beads are prepared by reacting GBL with Amberlite IRN78 under conditions represented by Batch B2. GBL (36.9 g) is slowly added to a slurry of wet resin (Amberlite IRN78, 279 g) and water (about 200 g). The reaction is allowed to proceed for at least 1 hour at room temperature, with stirring. The product is vacuum filtered, then rinsed with several volumes of de-ionized water. The wet product is then placed in a 40° C. oven to dry overnight. 2.1 g of dried GHB resinate beads are then administered to each of 6 beagle dogs, fasted and weighing approximately 10-12 kg, by oral gavage. Blood is sampled at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 10 h for determination of plasma GHB content.

Example 4

Amberlite IRN78, a hydroxide form Type 1 anion exchange resin, is charged to a vessel and contacted with a 1M solution of sodium oxybate in a 2:1 stoichiometry to resin equivalents. After about 2 hours of equilibration, the mixture of sodium oxybate and sodium hydroxide is filtered from the resulting resinate. A sample of the solution is titrated to determine sodium hydroxide content, and then an equivalent amount of calcium oxybate is charged to the solution to precipitate calcium hydroxide. The calcium hydroxide is filtered from the solution of sodium oxybate, and the recovered sodium oxybate solution is returned to the equilibration tank and contacted with the wet resinate for 2 hours. The resinate is then filtered, and filtrate is recovered. The recovered filtrate is processed with calcium oxybate as in the first step, and set aside for future use. The resinate product is washed with several volumes of de-ionized water, and then dried.

Example 5

Cholestyramine (chloride form) is charged to a vessel and contacted with 1M sodium bicarbonate in a 2:1 stoichiometry (bicarbonate to resin). Five cycles of batch equilibration (2 h each) are conducted. The solutions in each cycle are not recycled, and resinate is rinsed with 2 volumes of de-ionized water between each cycle.

The wet, bicarbonate-exchanged resin is then contacted with 1M sodium oxybate in a single equilibration step in a 2:1 molar ratio of oxybate to resin. After 2 h, the resinate is filtered, and filtrate collected. Separately, the GHB-resinate is then washed with several volumes of de-ionized water. A sample of the first filtrate is titrated for bicarbonate content, and then a stoichiometric amount of calcium oxybate is added to the batch filtrate. The precipitated calcium carbonate is removed by filtration of the suspension, and the sodium oxybate solution is recovered and stored for future use.

Example 6

The above examples can involve difficult separation steps, as precipitated calcium carbonate is a thick slurry of fine particles at the concentrations used. In this example, filtration is avoided by use of a reaction in which the byproduct forms carbon dioxide rather than a precipitate.

The wet, bicarbonate-exchanged resin of Example 5 is contacted with 1M sodium oxybate in a single equilibration step in a 2:1 molar ratio of oxybate to resin. After 2 h, the resinate is filtered, and filtrate collected. Oxybate is recovered and bicarbonate is removed from the filtrate by addition of a stoichiometric amount of sodium hydroxide such that the bicarbonate is converted to carbonate by the reaction: $NaOH+NaHCO_3 \rightarrow Na_2CO_3+H_2O$. The pH drives this reaction to completion.

Next, GBL is added at a 1:1 stoichiometry. Sodium carbonate reacts with the GBL with the evolution of carbon dioxide gas, which drives the reaction to completion: $2\ GBL+Na_2CO_3+H_2O \rightarrow 2\ Na\text{-}GHB+CO_2(g)$. Optionally, a small excess of sodium hydroxide can be added to avoid conversion to bicarbonate during the reaction. This overall process avoids the filtration of carbonate, recovers all the sodium as unexchanged sodium oxybate, and replaces the exchanged sodium oxybate with new oxybate derived from GBL.

Example 7

Soy protein isolate is compressed into oblong or oval tablets of approximately 1000 mg, using compression aids such as fillers, microcrystalline cellulose, and lubricants as required. The tablets are enteric coated separately with two different polymers to achieve dissolution and release of the soy protein isolate in the jejunum and ileum. One batch is

coated with Eudragit L30D-55 (jejunum-targeted), and the other is coated with Eudragit L100 (ileum-targeted). At least two of each kind of tablets are taken with one dose of GHB-resinate (35.7 mEq of resinate equivalent to 4.5 g oxybate) in a glass of water. This provides at least 36 mEq of amino acid content, as the protein is hydrolyzed. By releasing the protein in the small intestine rather than stomach, complete and rapid digestion is avoided. Instead, the protein is digested to amino acids more gradually as it transits the small intestine and as the tablet disintegrates. The amino acids are therefore available to facilitate exchange of the GHB-resinate taken concomitantly.

We claim:

1. A formulation of gamma-hydroxybutyrate comprising:

a plurality of immediate release particles comprising gamma-hydroxybutyrate;

a plurality of modified release particles comprising gamma-hydroxybutyrate;

a viscosity enhancing agent; and

an acid;

wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.

2. The formulation of claim **1**, wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof.

3. The formulation of claim **1**, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

4. The formulation of claim **1**, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate.

5. The formulation of claim **4**, wherein the lubricant is magnesium stearate.

6. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate.

7. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 4.0 g, about 6 g, about 7.5 g or about 9 g of sodium gamma-hydroxybutyrate.

8. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 6 g of sodium gamma-hydroxybutyrate.

9. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 7.5 g of sodium gamma-hydroxybutyrate.

10. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 9 g of sodium gamma-hydroxybutyrate.

11. The formulation of claim **1**, wherein 8 h after administration of the formulation provides a blood concentration ranging from 10 mg/L to about 40 mg/mL.

12. The formulation of claim **1**, wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL.

13. The formulation of claim **1**, wherein the formulation is a multiparticulate composition.

14. A unit dose comprising a formulation of gamma-hydroxybutyrate,

wherein the formulation comprises:

a plurality of immediate release particles comprising gamma-hydroxybutyrate;

a plurality of modified release particles comprising gamma-hydroxybutyrate;

a viscosity enhancing agent; and

an acid;

wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.

15. The unit dose of claim **14**, wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof.

16. The unit dose of claim **14**, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

17. The unit dose of claim **14**, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate.

18. The unit dose of claim **17**, wherein the lubricant is magnesium stearate.

19. The unit dose of claim **14**, wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL.

20. The unit dose of claim **14**, wherein the unit dose comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate.

21. The unit dose of claim **14**, wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 6 g of sodium gamma-hydroxybutyrate.

22. The unit dose of claim **14**, wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 7.5 g of sodium gamma-hydroxybutyrate.

23. The unit dose of claim **14**, wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 9 g of sodium gamma-hydroxybutyrate.

24. The unit dose of claim **14**, wherein the unit dose is a sachet.

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CERTIFICATE OF SERVICE

I hereby certify that on November 12, 2024, I caused the foregoing document to be electronically filed with the United States Court of Appeals for the Federal Circuit through the Court's CM/ECF system. All parties are represented by registered CM/ECF users and will be served by the CM/ECF system. Pursuant to agreement, the confidential version of the foregoing was also served on counsel for all parties by electronic mail.

/s/ Gabriel K. Bell
Gabriel K. Bell